

TERTIARY N-ACYL PHOSPHORAMIDATES -

A MECHANISTIC STUDY OF THEIR FORMATION AND COLLAPSE

IN REACTIONS WITH NUCLEOPHILES

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by

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to my family

CONTENTS

ABSTRACT	i
ACKNOWLEDGEMENTS	ii
PUBLICATIONS	iii
CHAPTER 1 INTRODUCTION	1
1.1 GENERAL	1
1.2 ELECTRONIC AND STRUCTURAL FEATURES.	3
1.3 FRAGMENTATION PATTERNS	4
1.4 NUCLEOPHILICITY OF THE MIXED PHOSPHORAMIDE-CARBOXAMIDE ANION	5
1.5 NEUTRAL AND ACID CATALYSED SOLVOLYTIC BEHAVIOUR	6
CHAPTER 2 RESULTS AND DISCUSSION	8
2.1 N-PHOSPHORYLATION OF CARBOXAMIDE ANIONS	8
2.2 BENZOYLATION OF N-SUBSTITUTED PHOSPHORAMIDATES IN THE PRESENCE OF A BASE	10
2.3 REACTION OF DIPHENYLKETENE WITH N-METHYL DIETHYLPHOSPHORAMIDATE	13
2.4 N-ACYLATION OF PHOSPHORAMIDE ANIONS	16
2.4.1 ESTER FORMATION	21
2.4.2 AMIDE AND IMIDE FORMATION	26
2.4.3 THE ROLE OF THE PHASE-TRANSFER CATALYST	34
2.4.4 THE ROLE OF THE MONOANION	39
2.4.5 PROPOSED MECHANISM OF NITROGEN GROUP TRANSFER	42
CHAPTER 3 REACTIONS OF MIXED IMIDES WITH GRIGNARD REAGENTS	53
3.1 INTRODUCTION	53
3.2 RESULTS AND DISCUSSION	58
CHAPTER 4 EXPERIMENTAL	65
4.1 GENERAL	65
4.2 PREPARATION OF SUBSTRATES	66
4.3 REACTIONS	71
4.3.1 REACTIONS DISCUSSED IN CHAPTER 2	71
4.3.2 REACTIONS DISCUSSED IN CHAPTER 3	79
APPENDIX	83
REFERENCES AND NOTES	91

ABSTRACT

Different synthetic approaches to tertiary mixed phosphoric-carboxylic imides(III) are discussed. The preparation of (III) via the N-acylation of phosphoramidates was investigated. The reaction of PhC(O)X ($\text{X} = \text{Br}, \text{Cl}, \text{F}$) with the conjugate base of $(\text{EtO})_2\text{P(O)NHMe}$ (IX) yields three products: PhCO_2Et (4), PhC(O)NHMe (5) and $(\text{PhCO})_2\text{NMe}$ (6). (5) and (6) are formed via the initial rapid formation of $(\text{EtO})_2\text{P(O)-NMe-C(O)Ph}$ (IIIe), while (4) results from the E1cB related reaction of $(\text{EtO})_2\text{P(O)}\bar{\text{NMe}}$ involving electrophilic assistance by PhC(O)X . The attack of various nucleophilic species at the mixed-imide (IIIe) was studied, and the possible mechanisms of the P-N bond cleavage, followed by the N-methyl transfer from the phosphoryl to the carbonyl centre are discussed.

The results of reactions of $(\text{RO})_2\text{P(O)-NMe-C(O)CH}_3$ ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$) with Grignard reagents reveal that carbon nucleophiles attack exclusively at the carbonyl centre of the substrate. The reluctance of these carbanions to attack at the phosphoryl electrophilic centre is not related to their steric requirements as methylmagnesium iodide and phenylmagnesium bromide show an equal preference for attack at the carbonyl centre. The direction of the reaction is attributed instead to the energetically unfavourable pseudorotation step in the oxyphosphorane which forms as an intermediate in the pathway proceeding via phosphoryl attack.

Preliminary crystal and molecular structure data of $\text{Ph}_2\text{P(O)-NMe-C(O)Ph}$ (IIIi) have been obtained.

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PUBLICATIONS

1. Alkylation of Ambident Ions Derived from Phosphoric-Carboxylic Imides. N-Benzoyl-0,0-Dimethyl-0-Ethyl Phosphorimidate and E/Z O-Ethyl-N(Dimethylphosphoryl)Benzimidate; V. Mizrahi, T. Hendrickse and T.A. Modro, *Can. J. Chem.*, 61, p. 118-123, (1983).

2. Phosphoric-Carboxylic Imides III. The benzylation of N-methyl diethylphosphoramidate and related anions; T.F. Hendrickse, V. Mizrahi and T.A. Modro, submitted for publication to *J. Org. Chem.*

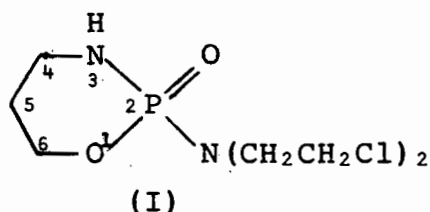
CHAPTER 1

Introduction

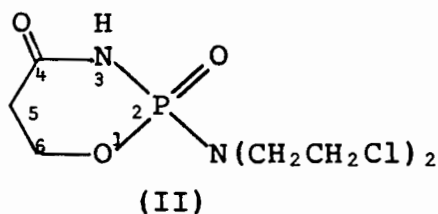
1. INTRODUCTION

1.1 GENERAL

In recent years cyclophosphamide (I) (2-bis(2-chloroethyl)amino-tetrahydro-2H,-1,3,2,-oxazaphosphorine 2-oxide)¹, has been found to exhibit clinical effectiveness against a relatively wide spectrum of human cancers.



However, (I) has little cytotoxic activity until it is activated to its metabolites. The mechanism of the *in vivo* activation of (I) to the cytostatically effective species has been a matter of considerable interest. In 1963, Brock and Hohorst² found that liver microsomal oxidation is in fact responsible for the activation process. Hill and coworkers³ have isolated a number of the active metabolites such as 4-ketocyclophosphamide (II) and 4-hydroxycyclophosphamide, as well as the ring opened carboxylic acid and aldehyde derivatives.

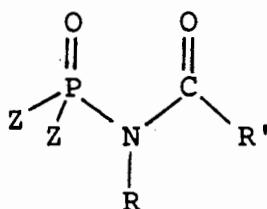


The isolation of (II) indicates that the metabolic reaction of cyclophosphamide involves mainly oxidation at the C-4 position on the oxazaphosphorine ring. This compound has been prepared independently and found to exhibit anti-cancer activity.

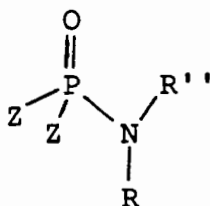
Our interest in (II) arises from the fact that it is one of the many biochemical examples which represent the incorporation of

the phosphoramidate and the carboxamide functional groups within the same molecular framework, as an OPNRCO moiety. An understanding of the interaction of these two functional groups in this moiety should lead to an improved understanding of the physiological activity of (II) and other related biochemical systems.

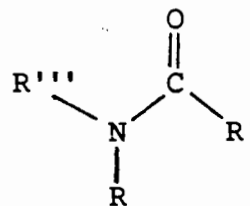
The N-acyl phosphoramidate system (III) succeeds in successfully combining the diverse features of both its parent phosphoric (IV) and carboxylic amide systems (V), as well as possessing some novel characteristics as a result of the resonance interaction of the nitrogen non-bonding electrons with the adjacent carbonyl and phosphoryl centres. For this reason they are excellent model compounds for investigations into the structural and chemical properties of the OPNRCO moiety.



(III)



(IV)



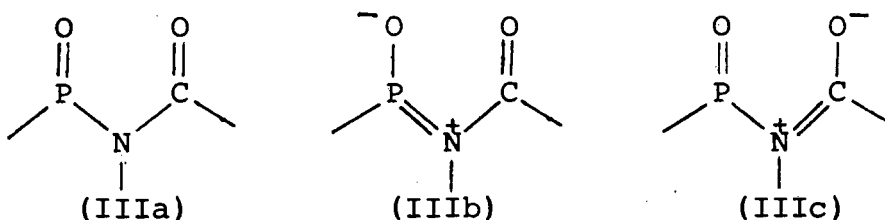
(V)

Although the amides (IV) and (V) have been extensively studied, the mixed-imides (III) are relatively new compounds and until recently reports in the literature covered mainly aspects relating to synthetic approaches and infrared studies. We have for some time been interested in these compounds and our

group has contributed considerably to a more detailed understanding of their chemical and structural properties. Investigations into their spectroscopic, nucleophilic, solvolytic and structural properties have been conducted.

1.2 Electronic and Structural Features

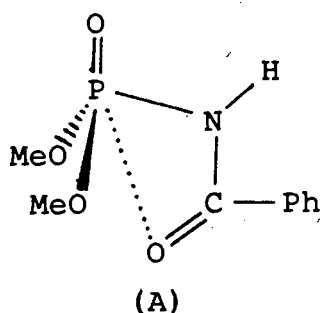
Infrared, ^1H and ^{13}C NMR features⁴ of the system (III) have revealed that the resonance interaction of the nitrogen non-bonding electrons occurs predominantly with the carbonyl rather than with the phosphoryl centre, i.e. (IIIc) is the major contributing canonical form to the overall resonance hybrid of the OPNRCO system.



However, this overall electronic distribution is largely affected by the electron-withdrawing effect of the phosphoryl substituent $\text{Z}_2\text{P}(\text{O})$, which weakens the basicity and the nucleophilicity of the nitrogen atom, while enhancing the electrophilicity of the carbonyl centre.

The molecular and crystal structure of N-benzoyldimethylphosphoramidate⁵ ($\text{Z}=\text{MeO}$, $\text{R}=\text{H}$, $\text{R}'=\text{Ph}$), has provided valuable information concerning the orientation of the carbonyl and phosphoryl functional groups. It was found that the OPNHCO moiety is planar and that there is incipient formation of the $\text{C}=\text{O} \cdots \text{P}^{\text{IV}}$ bond. This is possible because of the cis-trans arrangement of the phosphoryl and carbonyl groups. Structure A.

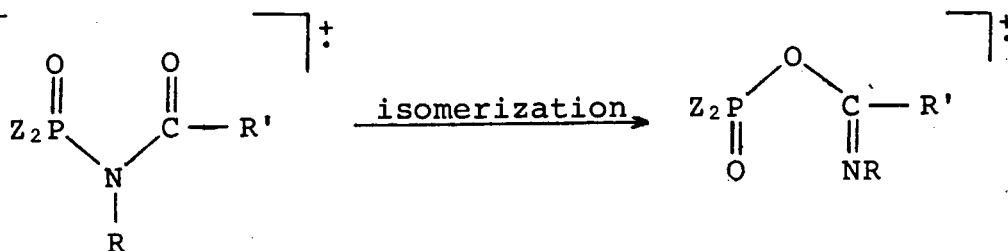
Structure A



1.3 Fragmentation Patterns⁶

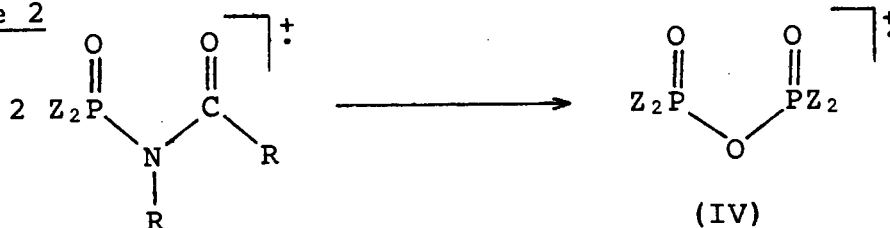
The main pathways of fragmentation of the mixed imides(III) indicate that the molecular ions involved are those in which the radical cationic centre is at carbonyl oxygen. They initially isomerise to give the corresponding o-phosphyl imidate, $Z_2P(O)-O-C(NR)R'$, which undergoes subsequent fragmentation via C-O fission (Scheme 1).

Scheme 1



Another typical feature of the tertiary substrates ($Z=O\text{-Alkyl}$, $R=Me$) under typical mass spectral recording conditions, is the formation of tetraalkylpyrophosphate(IV) via thermal disproportionation (Scheme 2).

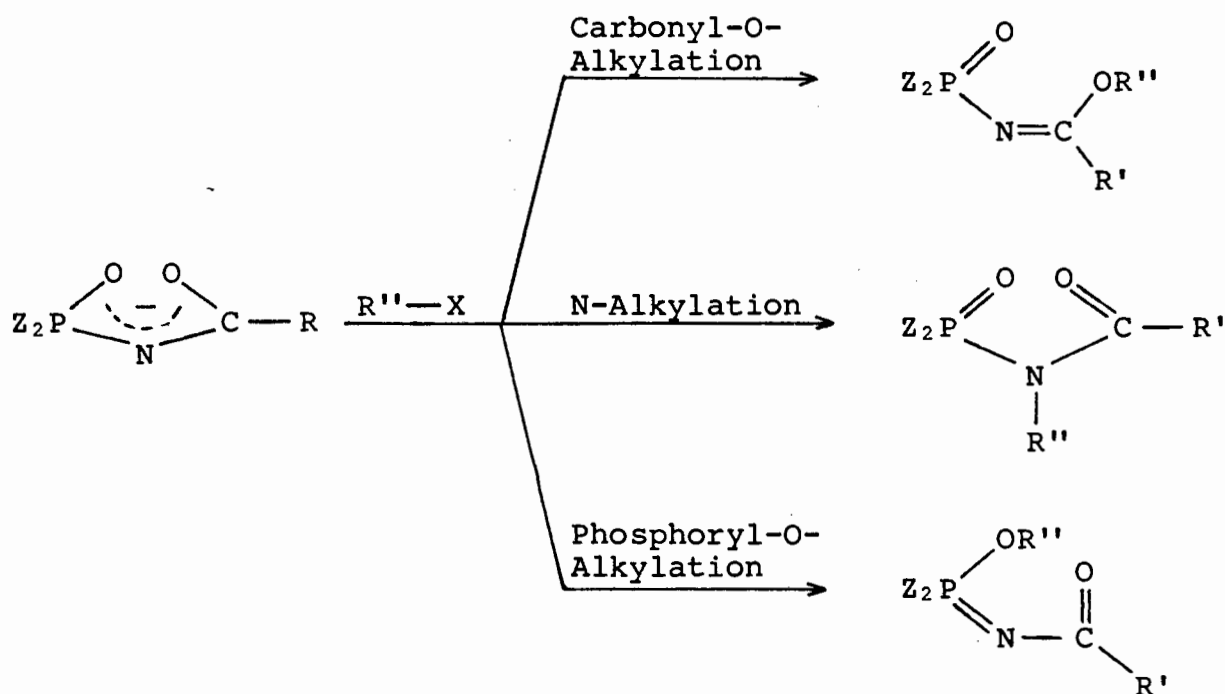
Scheme 2



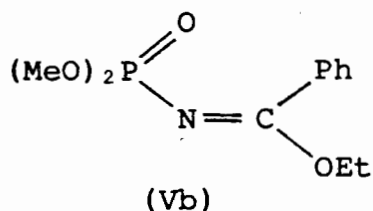
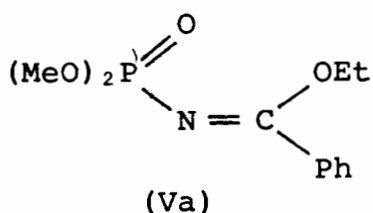
1.4 Nucleophilicity of the mixed phosphoramidate-carboxamide anion⁷

Alkylation of the sodium salts derived from the secondary derivatives of (III) (R=H), can in principal lead to the formation of three isomeric products (Scheme 3).

Scheme 3

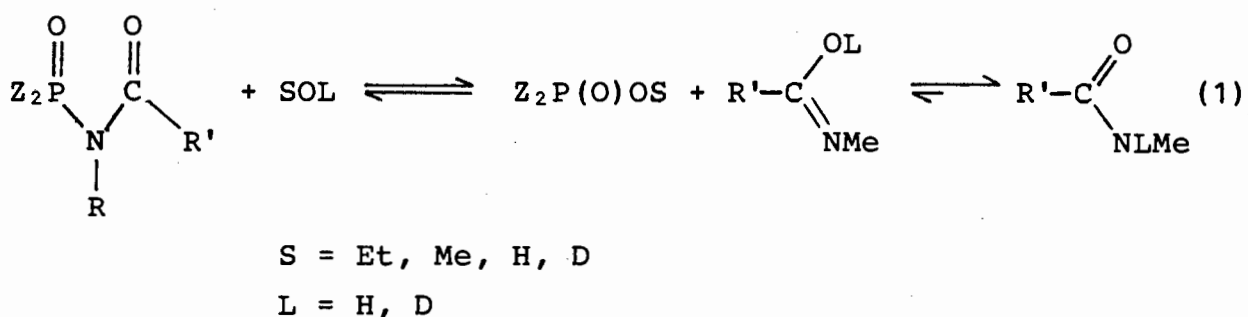


We have shown that the reaction conditions as well as the nature of the alkylating agent is important in determining the outcome of this reaction.⁷ The sodium salt of N-benzoyldimethylphosphoramidate was ethylated at low temperature with triethyloxonium ion to yield both the phosphoryl and carbonyl oxygen ethylated products, whereas the phase-transfer-catalysed reaction with ethyl iodide at elevated temperature yields only the carbonyl oxygen ethylated product as a pair of (E/Z) geometrical isomers (Va) and (Vb).

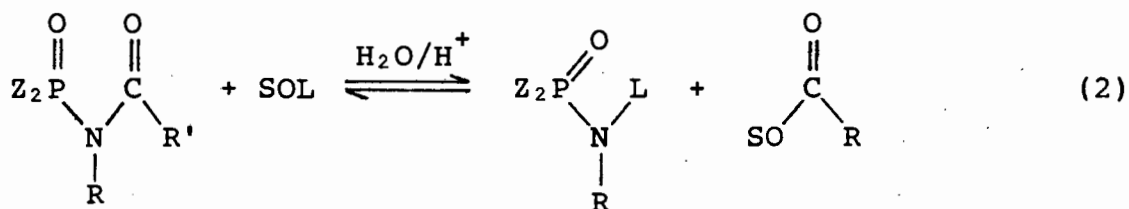


1.5 Neutral and Acid-Catalysed Solvolytic behaviour⁸

The mixed-imide system (III) exhibits different solvolytic behaviour, depending upon whether neutral or acidic conditions are used. Under neutral conditions, where the behaviour is largely determined by the relative electrophilicity of the two acyl centres, P-N cleavage is observed and it is argued that the process involves an oxyphosphorane intermediate (equation 1).



Under acidic conditions, the C-N bond becomes susceptible to solvolysis because of carbonyl oxygen protonation and the significant electron-withdrawing effect of the N-phosphoryl substituent (equation 2). The P-N bond is resistant to solvolysis under acidic conditions.



Because of the suitability of (III) as a model system, it is important that a convenient synthetic pathway leading to its formation be found. The first of these compounds to be synthesized is N-benzoylphosphoramidic acid (Z=OH, R=H, R'=Ph), by Titherley and Worral⁹ in 1909. A review of the literature

reveals that although there are a number of synthetic approaches whereby secondary derivatives of (III) (R=H) are readily accessible,¹⁰ a reliable synthesis for their tertiary analogues (R = Alkyl, Aryl) is lacking. The preparation of tertiary mixed phosphoric-carboxylic imides was thus investigated with the aim of firstly, establishing the limitations of those approaches proposed in the literature and secondly, suggesting alternative pathways via which these compounds may be synthesised.

CHAPTER 2

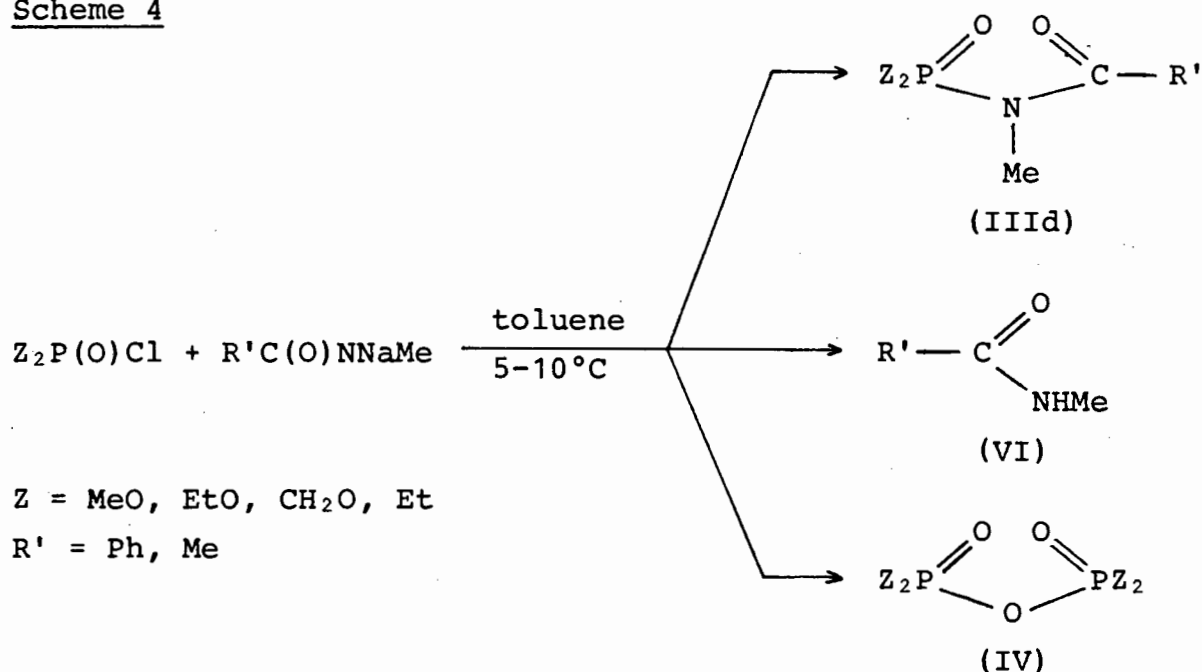
Results and Discussion

2. RESULTS AND DISCUSSION

2.1 N-phosphorylation of carboxamide anions

The N-phosphorylation of carboxamide anions is the most recent approach to the synthesis of tertiary mixed-imides and was first reported in the literature by Mizrahi and Modro.⁶ The amide anion is generated by the reaction of the neutral amide with finely divided sodium metal in refluxing toluene. When the phosphorylating agent is added to the salt suspension at a temperature of 5-10°C, as initially reported,⁶ the reaction is complicated by the side reactions indicated in Scheme 4.

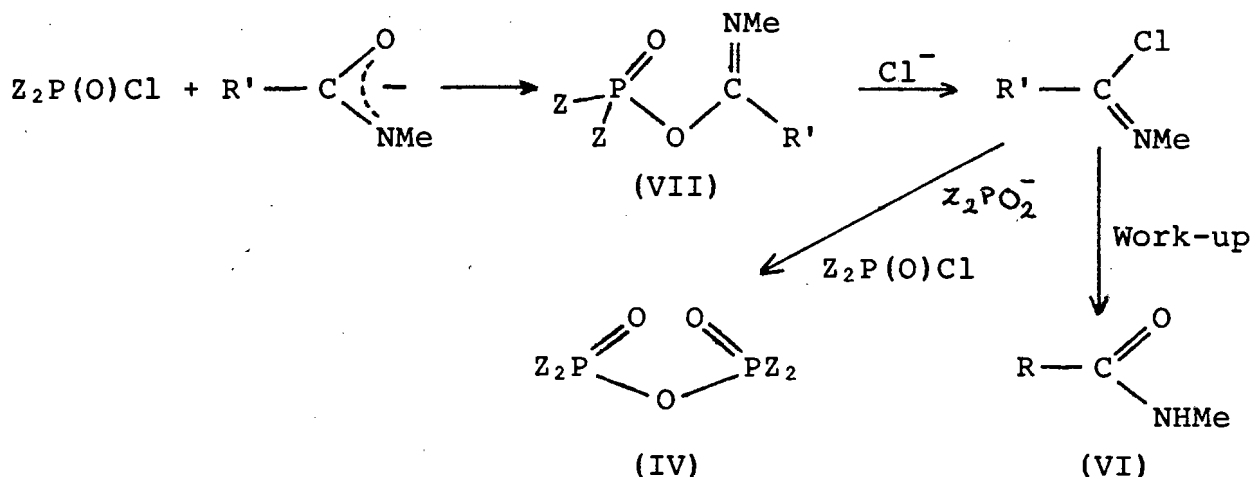
Scheme 4



(IV) is only observed for $\text{Z} = \text{MeO, EtO}$.

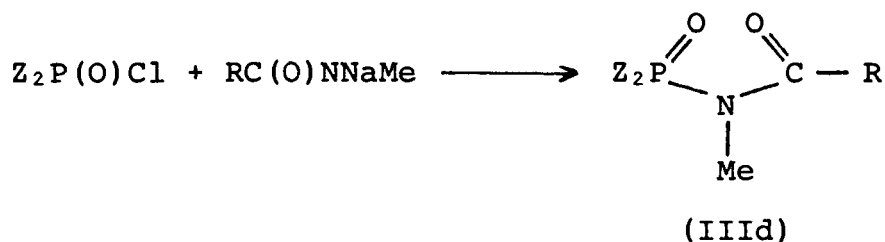
The formation of the carboxamide (VI) and tetraalkylpyrophosphate (IV) products lead to a lowering of the mixed imide yield to approximately 35%. The formation of these two products have been speculatively attributed to the collapse of the kinetically controlled O-phosphoryl imidate product (VII) via chloride ion induced C-O cleavage as illustrated in Scheme 5.¹¹

Scheme 5



We have subsequently found that the efficiency of this reaction as a synthetic approach to the mixed-imides (III), is dependent on the temperature at which the reaction is carried out. It would appear that higher temperatures are favourable, however attempts to synthesise these compounds under conditions of heating under reflux have been completely unsuccessful. These observations are not surprising as (III) is in fact the thermodynamically controlled product and it is logical to assume then that it can be prepared in optimum yield at some threshold reaction temperature which varies with the nature of the groups Z, R and R''. The results of some reactions are tabulated below together with some reactions previously attempted.⁶

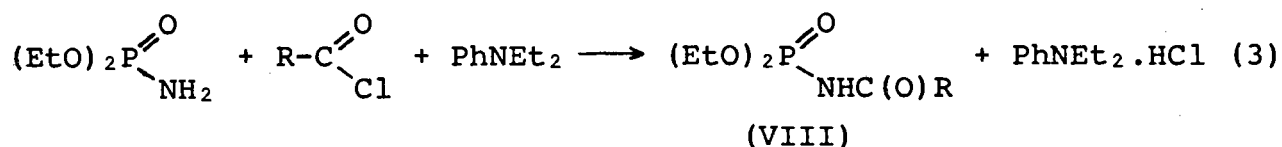
Table 1



Z	R	Temp. °C	% Yield of (IIId)
EtO	Ph	5-10	30
EtO	Ph	25-30	40
MeO	Me	5-10	38
MeO	Me	35-40	69
MeO	Me	50-55	75
Ph	Ph	5-10	18
Ph	Ph	40-45	50

2.2 Benzoylation of N-substituted phosphoramidates in the presence of a base

Alimov *et al* reported¹² that mixed imides can be conveniently prepared by the reaction of phosphoramidates with acid chlorides in the presence of a suitable base. In the study made of the reaction of the acid chlorides of acetic, butyric and isobutyric acids with diethylphosphoramidate using diethyl aniline as a base, the authors claim that the reaction proceeds via a simple substitution to yield the corresponding acylamido-phosphates(VIII) according to equation 3.



R = CH₃ (1), C₃H₇ (2), (CH₃)₂CH- (3).

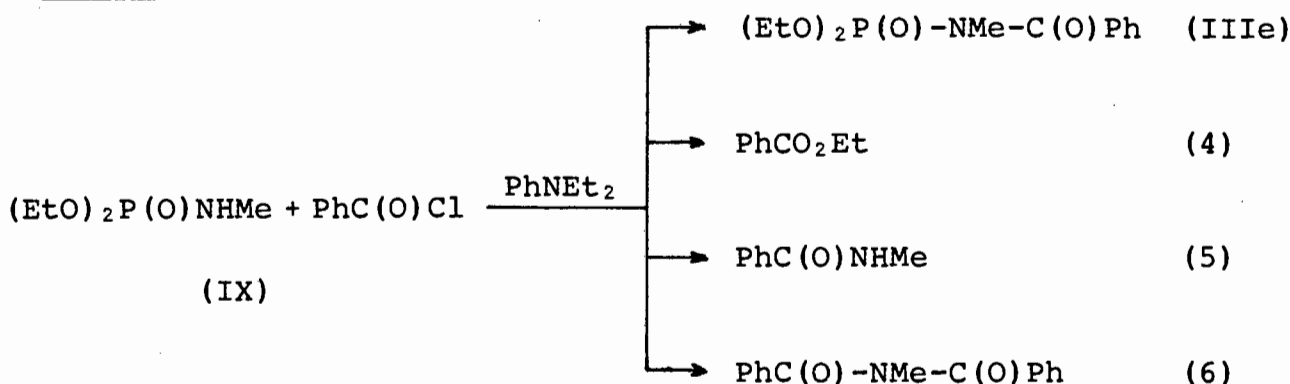
The yields of acylamidophosphates (1-3), formed as a result of this reaction, are respectively 72, 67 and 64%. Although no specific mention is made of the fact that higher yields are recorded for the less bulky acylating agents, we believe that this might be a significant observation. Also noteworthy is the fact that conditions of higher temperatures were employed when the more bulky acylating agents were used.

There is no obvious reason which suggests that this reaction should not be possible with N-substituted phosphoramidates and thus constitute a synthesis for 3° N-acylphosphoramidates. Preliminary results of such reactions are contradictory. On the one hand, it is claimed¹³ that the reaction of N-phenyldiethylphosphoramidate with benzoyl chloride or benzoic anhydride in pyridine, gave benzanilide in 30 and 23% respectively, while the reaction of N-isopropyldimethylphosphoramidate and benzoyl chloride in the presence of triethylamine yields N-benzoyl-N-isopropylphosphoramidate.¹⁴

Our attempts at benzoylating N-methyldiethylphosphoramidate (IX) was modelled upon the procedure described by Alimov *et al*¹² which utilises N,N-diethylaniline as a base. Because of steric crowding at the nitrogen atom in (IX), we anticipated that substitution would be less favourable than when nitrogen is unsubstituted. We thus carried out the reaction at different temperatures of 20, 55 and 75°C.

The reaction mixtures obtained after ether washing, filtration and evaporation, were periodically monitored by thin layer chromatography and ¹H NMR spectroscopy. Scheme 6 summarises the outcome of the reaction.

Scheme 6



Products (IIIe), 5 and 6 were readily identified by their ^1H NMR N-Methyl resonances at $\delta 3.15$ (d, $J_{\text{H,P}}=8\text{Hz}$)⁶, $\delta 2.96$ (d, $J_{\text{H,H}}=5\text{Hz}$) and $\delta 3.51$ respectively. These resonances are excellent probes by which the formation and decomposition of these compounds can be monitored. The ester product (4) could only be identified by its $-\text{OCH}_2$ resonances at $\delta 4.38$ (q, $J_{\text{H,H}}=6\text{Hz}$) at relatively high concentrations, owing to partial signal overlap with the methylene proton resonances of the phosphoramidate substrate (IX) and those of the mixed-imide (IIIe).

Since no detectable reaction is observed after a considerable period of time at 20°C , the reaction was repeated at elevated temperatures. The reaction at 55°C yields 16% (IIIe) after stirring for 1.5 h. The concentration of (IIIe) increases to a maximum of 26% after 4 h at this temperature, whereafter it decreases with concomitant increase in the concentration of products (4), (5) and (6). The final product mixture obtained after 20 h consists predominantly of (4) (ca. 40%) and (5) (ca. 33%). The outcome of the reaction conducted at 75°C is similar, yielding 27% of (IIIe) after 1 h. Further heating (20 h) leads to the total disappearance of this compound

and the formation of (4), (5) and (6) as the major reaction products.

Another very obvious feature of the ^1H NMR spectrum after 20 h at 75°C is the unusually low integration of the O-CH_2 protons of (IX) and (IIIe). The integration ratio of the total methylene proton to the total aromatic proton resonances suggests a considerable loss of the ethyl groups.

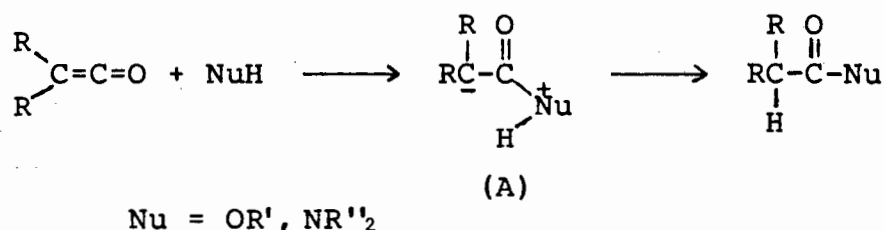
From these observations it is clear that although the reaction between phosphoramidates and acid chlorides in the presence of base is a suitable synthetic approach to secondary mixed imides, the same is not true for the formation of their tertiary analogues.

The implications of the observations made in these reactions are discussed at a later stage.

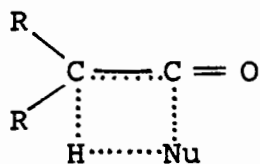
2.3 Reaction of diphenylketene with N-methyldiethylphosphoramidate

Ketene has been used extensively in the acetylation of alcohols, amines and other weak acids, while acylation with ketene derivatives has received much less attention. It was previously assumed that the acylation of weak acids (NuH) by ketene and its derivatives occurs via a two-step process involving an ionic intermediate (A) as shows in Scheme 7.

Scheme 7



However, subsequent kinetic investigations have demonstrated^{15,16} that an alternative one-step pathway involving a cyclic transition state (B) can also account for the acylation process.



(B)

The transition state can involve more than one molecule of the weak acid¹⁶ and it is apparent from the literature^{15,16a,b} that the steric bulk of the weak acid, the reaction conditions and a number of other factors are important in determining which of these two reaction pathways prevail.

The secondary phosphoramidates are weakly acidic¹⁷ and it is therefore possible to envisage the N-acylation of $\text{Z}_2\text{P}(\text{O})\text{NHMe}$ in a reaction with ketene or a derivative thereof.

We attempted the acylation of N-methyldiethylphosphoramidate (IX) with diphenylketene. This ketene was selected for the investigation because of the relative ease with which it can be prepared¹⁸ as well as its slow rate of dimerization. Staudinger has shown that there are wide differences in the reaction rates of different alkylketene derivatives and according to his qualitative sequence, diphenylketene appears to be the most reactive e.g. diphenyl > phenylmethyl > diethyl > dimethyl.¹⁹

Diphenylketene was prepared according to the method outlined by Staudinger¹⁸. The procedure involves the dehydrochlorination of diphenylacetylchloride with triethylamine. The ketene was not isolated but $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ was added directly

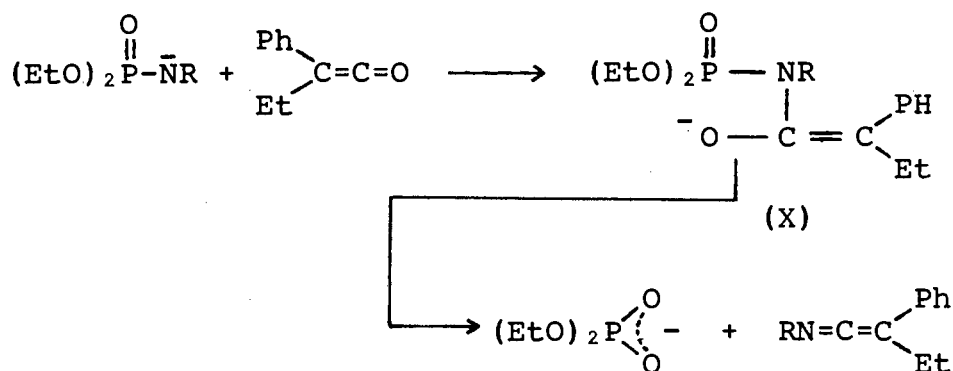
to the ethereal solution after removal of the triethylamine-hydrochloride by filtration. The reaction was carried out independently at room temperature and in refluxing ether.

^1H NMR analysis of the product mixtures after evaporation of ether indicated that no acylation had in fact taken place.

As this was merely a preliminary investigation, we are reluctant to generalise about the potential of the reaction involving N-acylation of N-alkylphosphoramidates by ketenes, as a possible synthesis for tertiary mixed-imides. It is worthwhile to consider the results of Wadsworth and Emmons.²⁰ They have shown that the reaction between N-alkylphosphoramidate anions and ketenes constitute a useful synthesis for ketenimines.

Three phosphoramidate anions, (R = phenyl, cyclohexyl, n-butyl), when treated with phenylethylketene, gave ketenimines in yields of 62, 58 and 18% respectively. It is proposed that the reaction proceeds according to Scheme 8, with the driving force for the collapse of (X) being provided by the excellence of diethylphosphate as a leaving group.

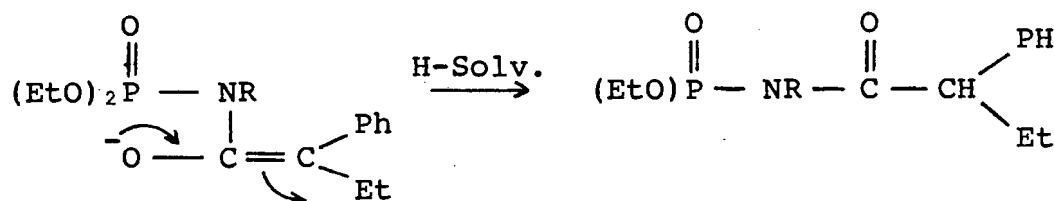
Scheme 8



The authors do not mention any other products observed in these reactions, nor do they comment on the poor yield of the ketenimine when R = n-butyl.

We would like to suggest that the collapse of (X) need not necessarily only proceed as in Scheme 8 but alternatively as in Scheme 9.

Scheme 9

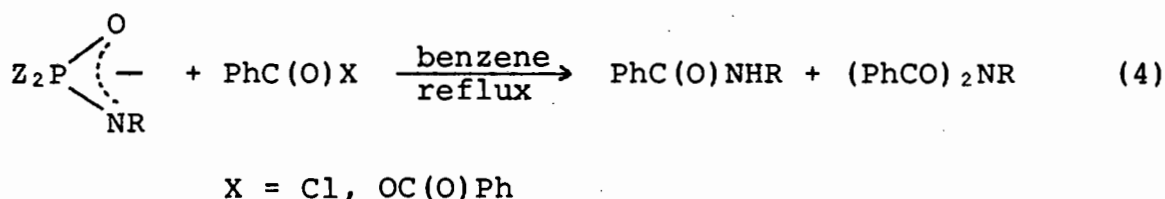


It is logical that the nature of the group R would be important in determining the pathway along which (X) collapses. Factors which increase the rotational energy barrier of the C-N bond, are expected to favour the collapse of (X) via the pathway proposed in Scheme 8. Thus, when R is a fairly bulky group, the yield of the corresponding ketenimine should be high. Alternatively, when R is less bulky, as in the case when R is the n-butyl group, the opposite should apply. The results of these reactions support this argument.

2.4 N-Acylation of phosphoramidate anions

Although early literature reports claim the facile acetylation²¹ and benzoylation²² of phosphoramidate anions, there does not appear to be any consistency in the outcome of these reactions. While Russian workers^{14,21} report the successful preparation of N-acetylphosphoramidates from the phosphoramidate anion and

acetyl chloride, Edmundson and Moran¹³ demonstrated the formation of N-substituted benzamides and dibenzamides by the benzylation (benzoyl chloride, benzoic anhydride) of a variety of phosphoramidate and phosphinamidate anions. The reaction appears to proceed via a nitrogen group transfer from the phosphorus to carbon as outlined in equation 4.

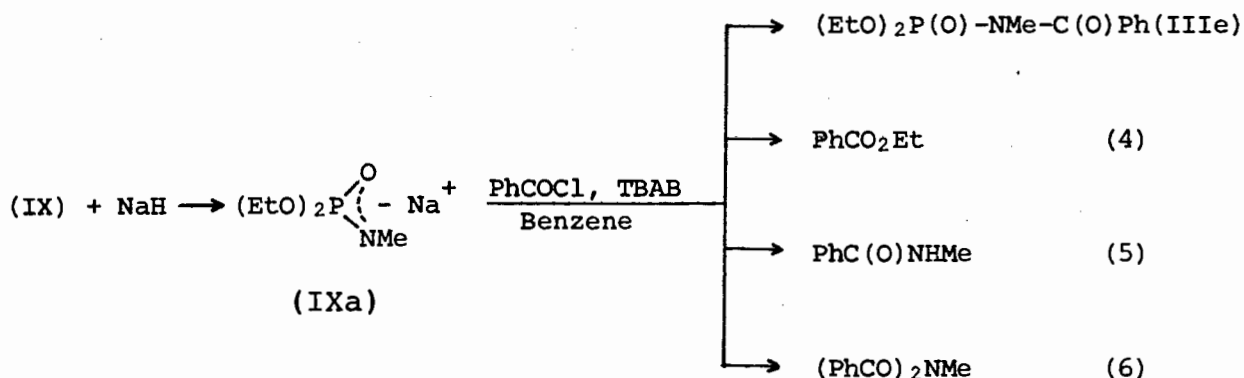


The authors forward rather speculative mechanistic proposals for the P-N cleavage reaction involved in equation 4. As these proposals are not substantiated in any way and as we did not agree with them (for reasons which shall be discussed later), a re-examination of the benzylation of N-methyldiethylphosphoramidate anion(IXa) was undertaken. The aim of this investigation was two-fold: firstly, to re-evaluate the potential of this reaction as a synthetic route to (EtO)₂P(O)-NMe-C(O)Ph (IIIe) and to test the generality of these reactions as synthetic approaches to tertiary mixed-imides(III). This was done essentially by manipulating reaction conditions in such a way as to favour the desired reaction. Secondly, we aimed at proposing a plausible mechanism to account for the formation of all the products in this reaction.

The reaction between the sodium salt of N-methyldiethylphosphoramidate(IX) and benzoyl chloride was carried out in benzene under similar conditions as those described by Edmundson and Moran,¹³ with the exception that a catalytic amount (5-10%) of

tetrabutylammoniumbromide (TBAB) was added to the reaction mixture in an effort to enhance the nucleophilicity of the phosphoramidate anion. Small fractions of the product mixture obtained after filtration and evaporation were periodically analysed by TLC and ^1H NMR. The products obtained are illustrated in Scheme 10.

Scheme 10



The reaction carried out at 6-8°C yields a small quantity (ca. 10%) of (IIIe), Figure 1. Owing to detection difficulties (partial ^1H NMR signal overlap, coincident Rf values of (4) and PhC(O)Cl, we were unable to ascertain whether or not the ester was formed at low temperature (6-8°C). Warming to room temperature results in the gradual appearance of (4) and (5). Heating under reflux leads to an increase in the concentrations of (4), (5) and (6) at the expense of both (IIIe) and (IXa). Prolonged heating (> 40 h) results in the complete disappearance of (IIIe) and an increase in the concentration of the imide (6). In addition, the ^1H NMR spectrum of the final product mixture (46 h under reflux) (Figure 2) revealed a 30% loss of ethyl groups (not shown in Scheme 10). These observations completely parallel those of the experiments discussed earlier (2.2). The quantitative outcome of the benzylation of (IX) is clearly

Figure 1: N-benzoylation of N-methyl diethylphosphoramidate anion -
 ^1H NMR Spectrum of the product mixture after .5 h at low temperature (6-8°C)

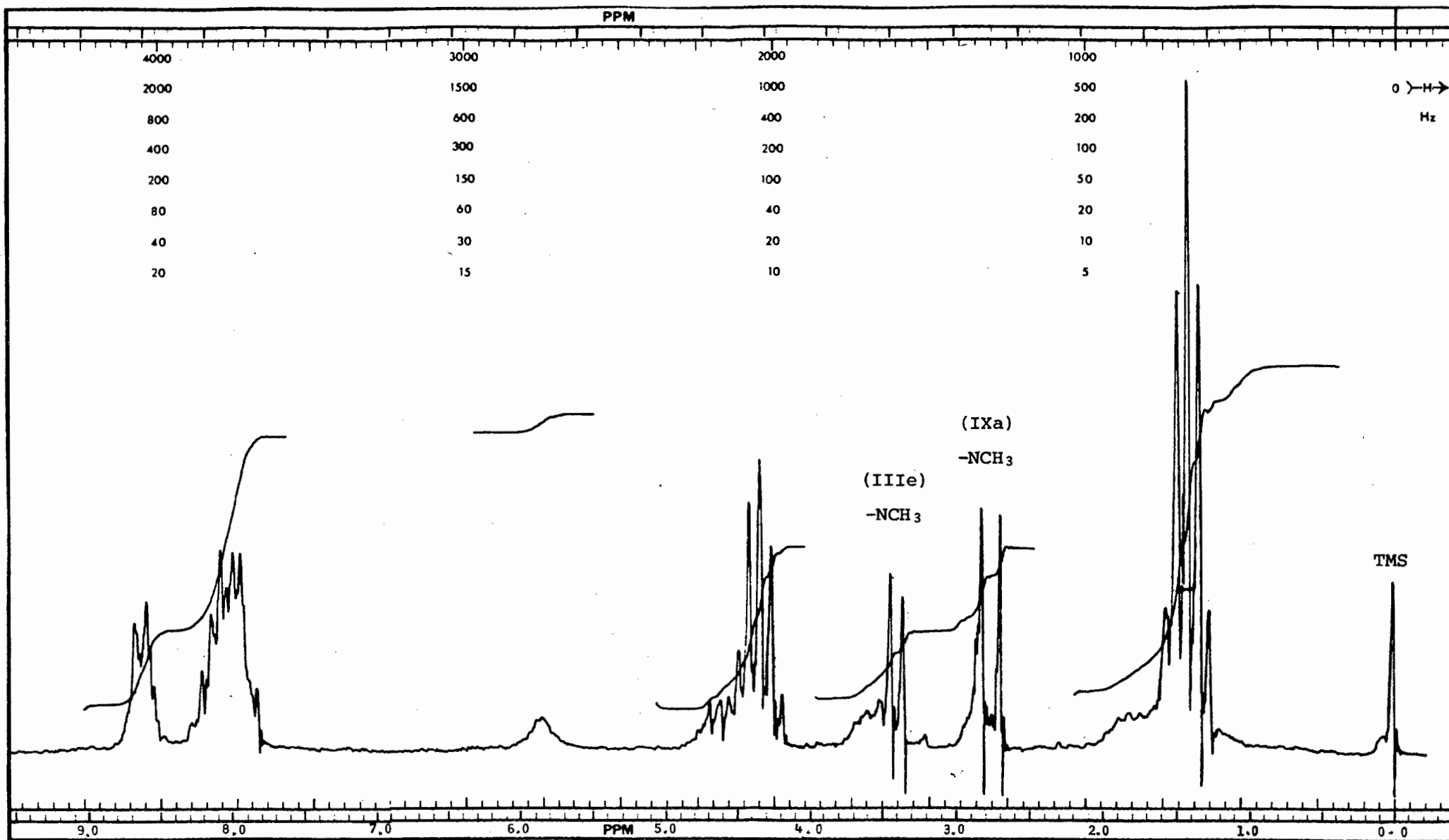
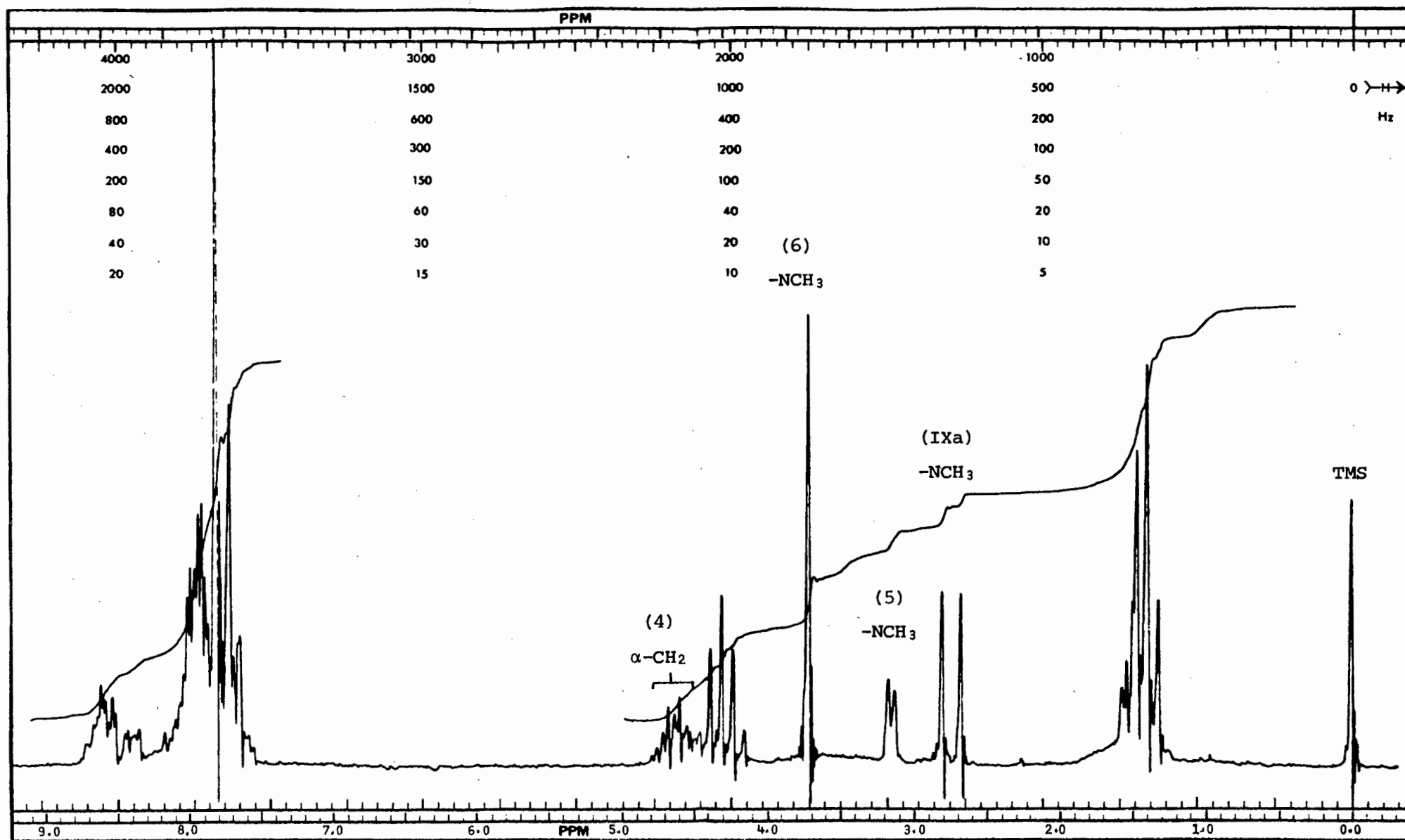


Figure 2: N-benzoylation of N-methyl diethylphosphoramidate anion -
 ^1H NMR Spectrum of the product mixture after heating under reflux (46 h)

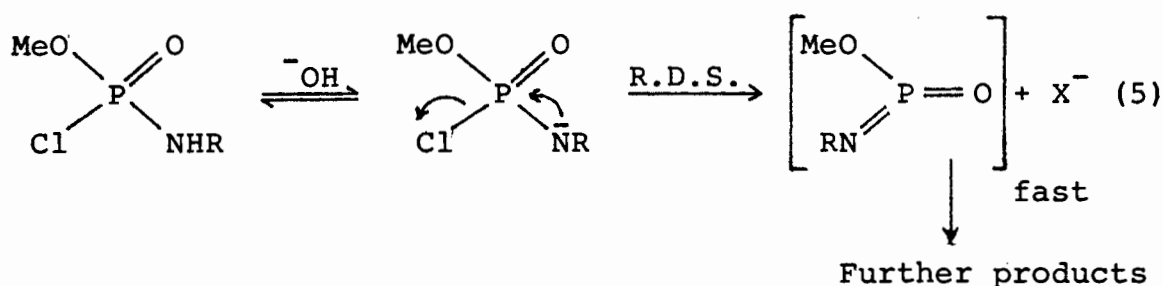


independent of the type of base employed (PhNEt_2 or NaH , Schemes 6 and 10 respectively). However, the reaction temperature is of prime importance in determining the relative concentrations of the four products. The nature of the reaction products indicates that the base-catalysed benzylation of (IX) follows two essentially independent pathways. The first pathway, accounting for the formation of the ester (4), involves a P-OEt cleavage reaction, whereas the second, accounting for the formation of the amide (5) and imide products (IIIe) and (6), involves a N-benzylation reaction. The mechanisms of these two reaction pathways are discussed individually.

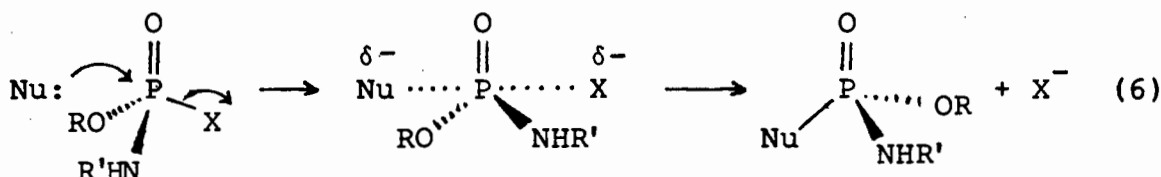
2.4.1 Ester Formation

The formation of ethylbenzoate (4) in the reactions outlined in Schemes 6 and 10 indicates that under basic conditions, N-methyldiethylphosphoramidate is capable of expelling ethoxide which can subsequently react with benzoyl chloride to give the ester product. This expulsion of ethoxide in many respects parallels the base-catalysed solvolysis of fully esterified derivatives of phosphoramidic acids. The latter reaction can involve either a unimolecular elimination from the conjugate base of the substrate (E1cB),²³ or a bimolecular substitution (BAC2) which is explicable in terms of a phosphorane intermediate.²⁴ In cases where the phosphoramidates bear good leaving groups, the mechanism is generally thought to be E1cB .²⁵ The most convincing evidence in support of this mechanism comes from the basic hydrolysis of phosphoramidic chlorides, which in contrast to neutral solvolysis proceed faster by a factor of 10^6 - 10^7 when the nitrogen

bears a proton than when it is fully substituted²⁶ (equation 5).

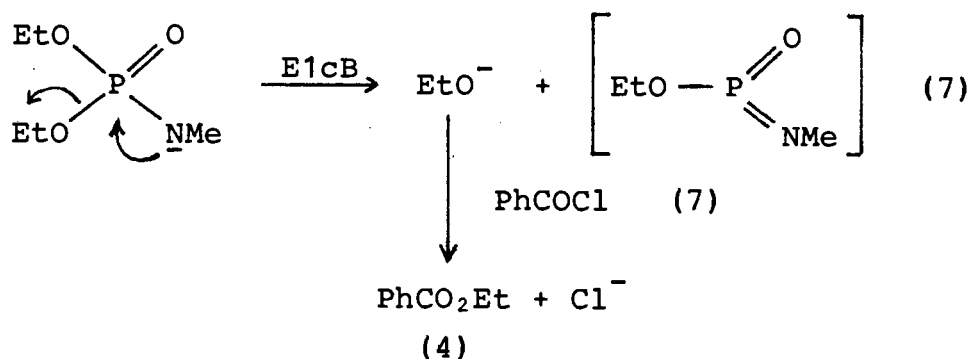


With poorer leaving groups than chloride ion however, the enhancements of the rates of hydrolysis of esters bearing a proton attached to nitrogen, are much smaller, and evidence has been accumulated by Hamer and Tack²⁴ to imply that base catalysed nucleophilic substitution proceeds via a BAc2 rather than an E1cB process (equation 6).



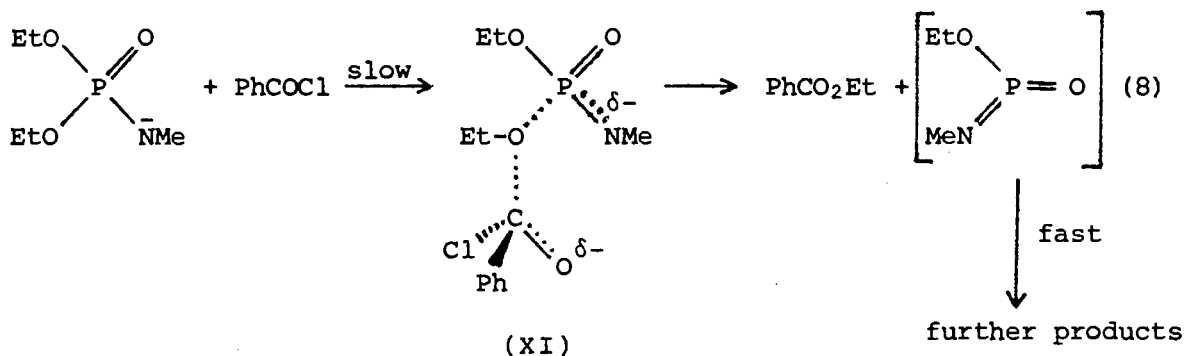
For reasons which will now be discussed, we believe that expulsion of ethoxide from (IX) under basic conditions discussed in sections 2.2 and 2.4, cannot be entirely attributed to the operation of either of these two mechanisms.

The observation that the formation of the ester (4) from the conjugate base of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ occurs in media that are deficient of nucleophiles capable of affecting P-OEt cleavage in the latter, enables us to exclude immediately the participation of a BAc2 mechanism. This would tend to favour an elimination type mechanism which could be represented by the equation (7) analogous to equation (5).



In view of the poor leaving ability of ethoxide ion ($\text{pK}_a \sim 16$), it is unlikely that this mechanism is purely unimolecular.

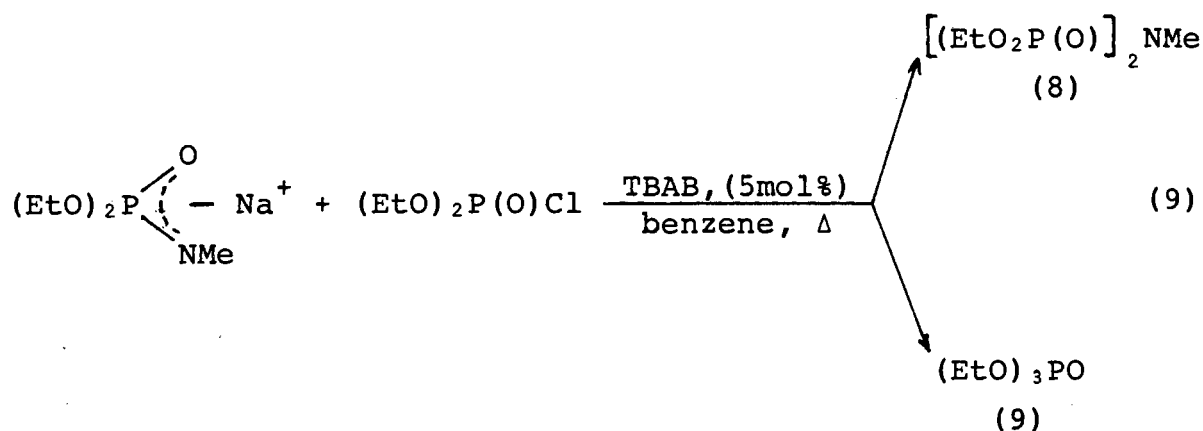
We propose that the rate determining P-OEt cleavage step in the phosphoramidate anion is one which involves electrophilic assistance by the benzoylating agent. It is suggested that the transfer of ethoxide proceeds through the transition state (XI) as in equation 8.



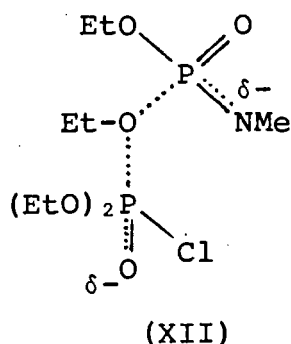
We have been able to gather much evidence in support of the proposed participation of an electrophile in the ethoxide ion expulsion from a number of control experiments that were conducted. It was found that in the absence of benzoyl chloride, prolonged heating of the sodium salt of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ in benzene under reflux, leads to no detectable loss of the ester function. The integration ratio of the ethyl protons to the N-methyl protons remained unchanged in

the ^1H NMR spectrum of the product mixture when compared with that of the substrate.

In a second control experiment the reaction was repeated replacing a benzoylating agent by a phosphorylating agent. It was found that besides yielding the expected imidophosphate product (8), the phase-transfer-catalyzed reaction of the salt of N-methyldiethylphosphoramidate with diethylphosphorochloridate also yields triethylphosphate (9), the phosphorus analogue of the ester (4), equation 9.



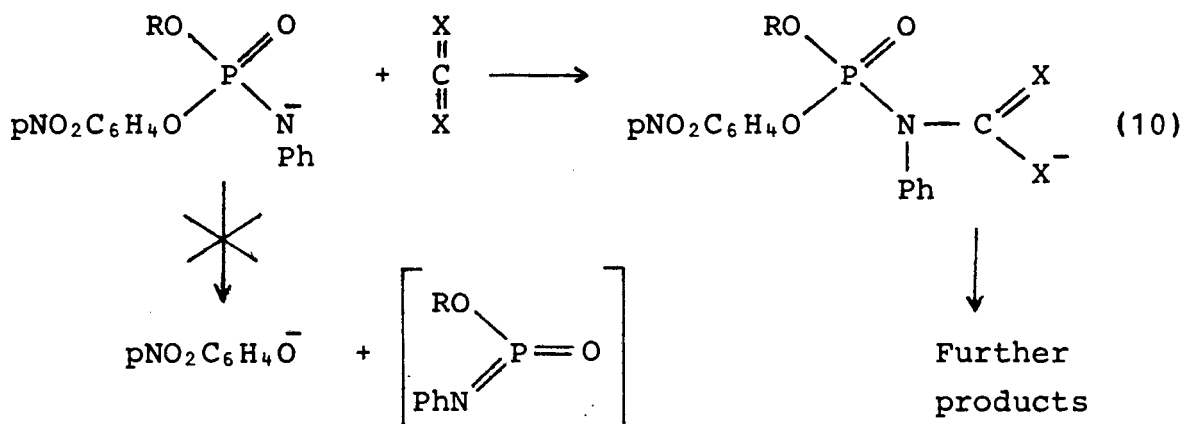
A transition state species (XII) similar to structure (XI) can be invoked in the explanation for the formation of triethylphosphate. Here electrophilic assistance in the ethoxide transfer is provided by the phosphoryl group as opposed to the carbonyl group.



Further evidence in support of the proposed mechanism would of course be the actual detection of the monomeric metaphosphorimidate species (7). However, since no phosphorus containing products other than the mixed-imide (IIIe) were isolated from the reaction mixtures (Schemes 6 and 10), the fate of this species is unknown. Monomeric metaphosphates are generally considered to be highly reactive species. They could polymerize or randomly phosphorylate components such as chloride ions and traces of moisture present in the reaction medium. The products thus formed would be either insoluble in organic solvents or acidic and as such would be difficult to isolate by silica-gel chromatography. We believe, however, that the formation of the metaphosphorimidate species (7) is related to the appearance of an unidentified N-methyl absorption (δ 2.74, d, $J=13\text{Hz}$) in the ^1H NMR spectra of fractions in which the ester (4), is also present. A review of the literature²⁷ has revealed no previous reports of the possible participation of E1cB elimination in the reactions of phosphoramidate anions in the presence of carbonyl and phosphoryl electrophiles.

In particular, Edmundson and Moran¹³ do not report the formation of either ethyl or phenyl benzoate in the study of the benzylation of $(\text{RO})_2\text{P}(\text{O})\bar{\text{N}}\text{R}$ anions ($\text{R} = \text{Et}, \text{Ph}$). It is not clear whether these esters are formed in the experiments described, as the product mixtures were generally incompletely resolved. We have established that the formation of the ester products is not dependent on the presence of a phase-transfer catalyst and hence our surprise at its absence from the product mixtures reported by these

authors. Similarly, Stec *et al*²⁸ do not report the loss of p-nitrophenoxide ion (a good leaving group), in the reaction of 2'-deoxynucleoside-3'-O(4-nitrophenyl)phosphor-anilidate anions with CX₂ (X = O, S) (equation 10).

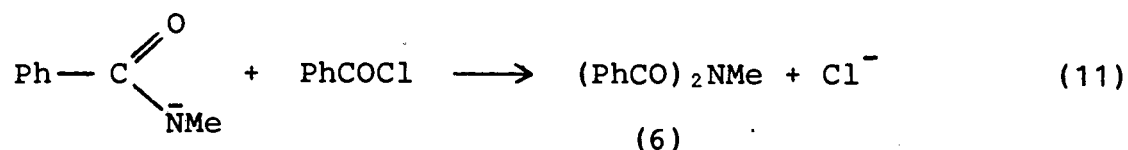


R = nucleoside

2.4.2 Amide and Imide Formation

From a consideration of the reaction products (IIIe), (5) and (6), it is obvious that all necessarily result from an initial N-benzoylation reaction. The mixed-imide (IIIe), is the first of these N-benzoylated products observed. The activation energy barrier for the nucleophilic substitution leading to its formation is relatively low as it is apparent even at very low temperatures (6-8°C). However, even under optimal reaction conditions, the yield of (IIIe) remains low, never exceeding 25%. Any attempt at increasing the yield of (IIIe) by increasing the temperature and the strength of the base (NaH vs PhNEt₂), leads to the formation of the carboxamide derivatives (5) and (6), and the subsequent gradual disappearance of the mixed-imide (IIIe).

The formation of the symmetrical-imide (6) can readily be explained by the base catalysed reaction of the amide (5) with excess benzoylating agent (equation 11).

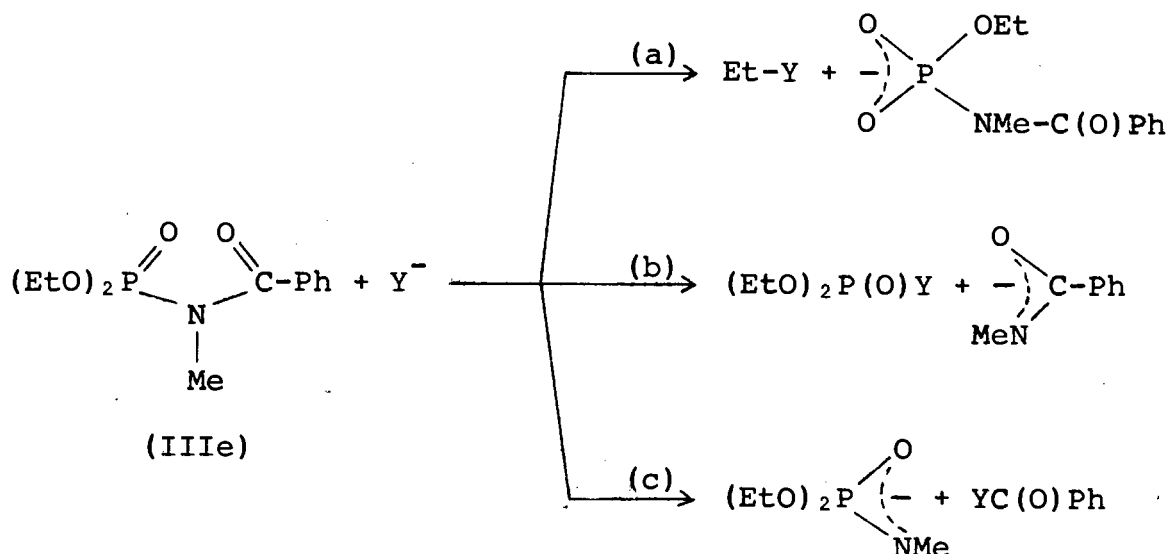


However, the mechanism for the formation of (5) itself, is less obvious. The process involves essentially a N-methyl transfer from the phosphorus in the substrate to the carbonyl carbon of the benzoylating agent. The fact that the mixed-imide (IIIe) is a logical intermediate in this transfer process, necessitated the design of a number of experiments aimed at establishing the involvement of this species in the formation of (5). The aim of these experiments may be more specifically defined as an attempt to outline precisely the mechanism of P-N bond cleavage in the mixed-imide (IIIe).

The possibility that this could in fact be due to a simple thermal decomposition was ruled out by the fact that the mixed-imide was found to be completely stable when heated for a prolonged period of time under reflux in benzene. It is logical to conclude then that decomposition of (IIIe) involves interaction with the nucleophilic species present in the reaction medium.

The reaction of (IIIe) with a nucleophile Y^- can occur via the three distinct pathways outlined in Scheme 11.

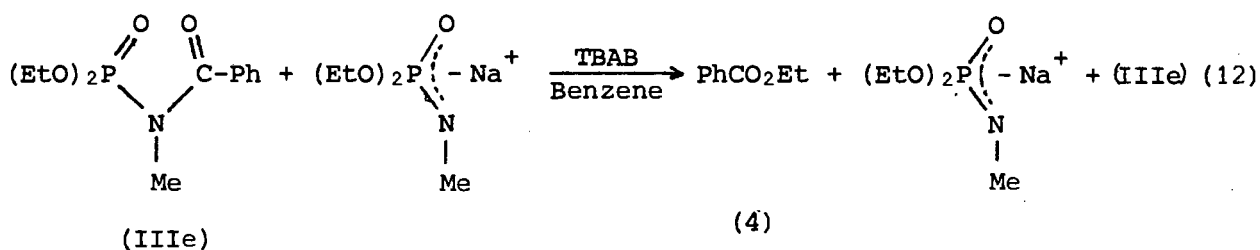
Scheme 11



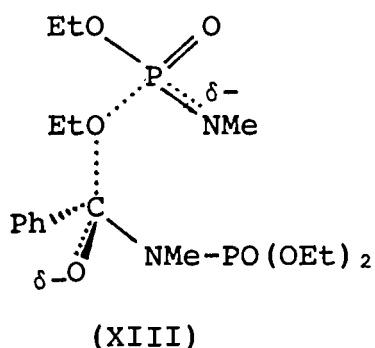
Nucleophilic attack can occur at the phosphoryl or the carbonyl centres or at the α -carbon of the ester groups attached to the phosphorus. Pathway (b) indicates that attack at the phosphoryl centre offers an avenue for the formation of N-methylbenzamide (5). For this reason, the reactivity of independently synthesized (IIIe) towards the various nucleophiles present in the reaction medium was investigated. Most of these reactions were carried out under dry nitrogen to preclude the possibility of hydrolysis of the substrate, which has been shown to proceed with exclusive P-N cleavage.⁸

Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$ with $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$

The phase-transfer-catalysed reaction of the salt $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ with an equimolar amount of (IIIe) in benzene under reflux, was conducted under conditions similar to those of the initial benzoylation reaction. The outcome of the reaction is summarised in equation 12.



The major product is the ester (4), which is presumably formed by ethoxide attacking at the carbonyl centre of (IIIe) via the transition species (XIII) as previously proposed (2.4.1).



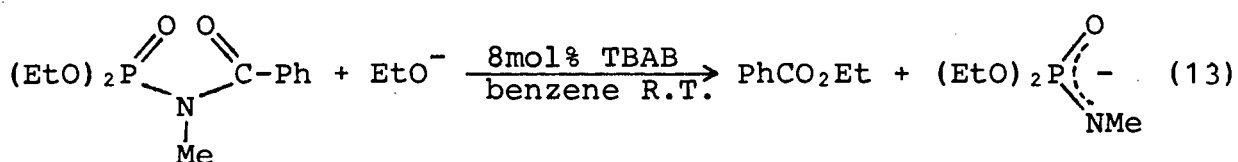
Although we do not doubt that the major pathway to the formation of the ester (4) involves benzoyl chloride (equation 8), the results of this reaction indicate that this secondary pathway could also lead to the formation of the ester (4).

The absence of the distinctive N-methyl triplet ($\delta 2.96$, $J_{\text{H,P}} = 9.5 \text{ Hz}$, 3H) of the imidophosphate $[(\text{EtO})_2\text{PO}]_2\text{NMe}$ (8), in

the ^1H NMR spectrum of the product mixture argues against nucleophilic attack by $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$ at the phosphoryl centre of (IIIe) (Scheme 11, pathway b). The greater electrophilicity of the carbonyl over the phosphoryl centre is illustrated by the absence of triethylphosphate (9) from the product mixture. It is also not surprising that the mixed-imide is not completely destroyed in this reaction as it is simply regenerated by attack of $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$ at the carbonyl centre of the substrate (IIIe).

Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$ with alkoxide ion

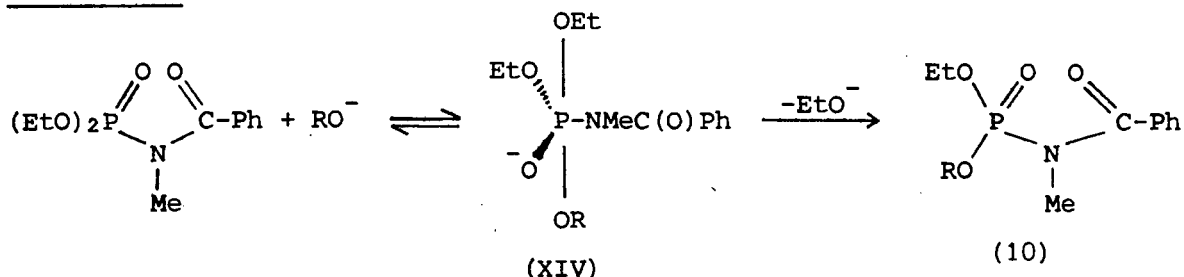
The reaction of (IIIe) with sodium ethoxide in benzene in the presence of 8 mol % TBAB is complete within 0,5 h at room temperature. The only observed products of the reaction are equimolar amounts of the ester (4) and the phosphoramidate anion which again result from direct attack of ethoxide ion at the carbonyl centre of (IIIe) (equation 13).



Nucleophilic attack by ethoxide ion at the phosphoryl centre of (IIIe) would give rise to the oxyphosphorane intermediate (XIV) (R=Et). The intermediate may collapse by P-OEt cleavage prior to the pseudorotation step to yield the transesterified product 10 (Scheme 12). This would amount to reversible attack of the ethoxide at the phosphoryl centre and the substrate (IIIe) would remain unchanged.

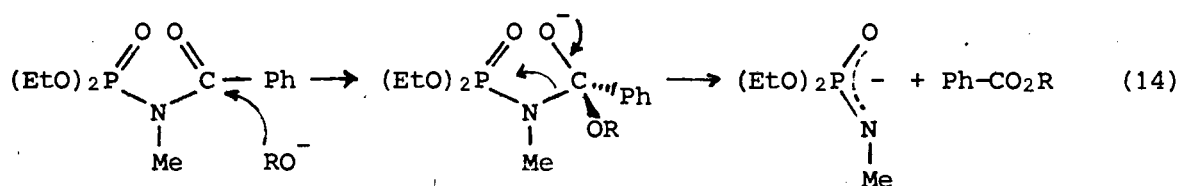
Alternatively the oxyphosphorane may collapse via expulsion of the conjugate base of (5). This involves a P-N cleavage mechanism which can only occur after the pseudorotation step.

Scheme 12



The possible participation of the transesterification reaction was ruled out by the outcome of the reaction of (IIIe) with sodium methoxide under the same reaction conditions. The total lack of methoxyl incorporation at the phosphorus (10, R=Me), argues against the formation of the oxyphosphorane (XIV) and hence alkoxide attack at the phosphoryl centre.

The exclusive formation of $(\text{EtO})_2\text{P}(\text{O})\bar{\text{N}}\text{Me}$ and PhCO_2R (R=Me, Et), and the absence of carboxamide products in both these reactions, is consistent with exclusive attack of alkoxide ion at the carbonyl centre of (IIIe) (equation 14).



These results parallel those outlined in equation 12.

Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$ with chloride ion

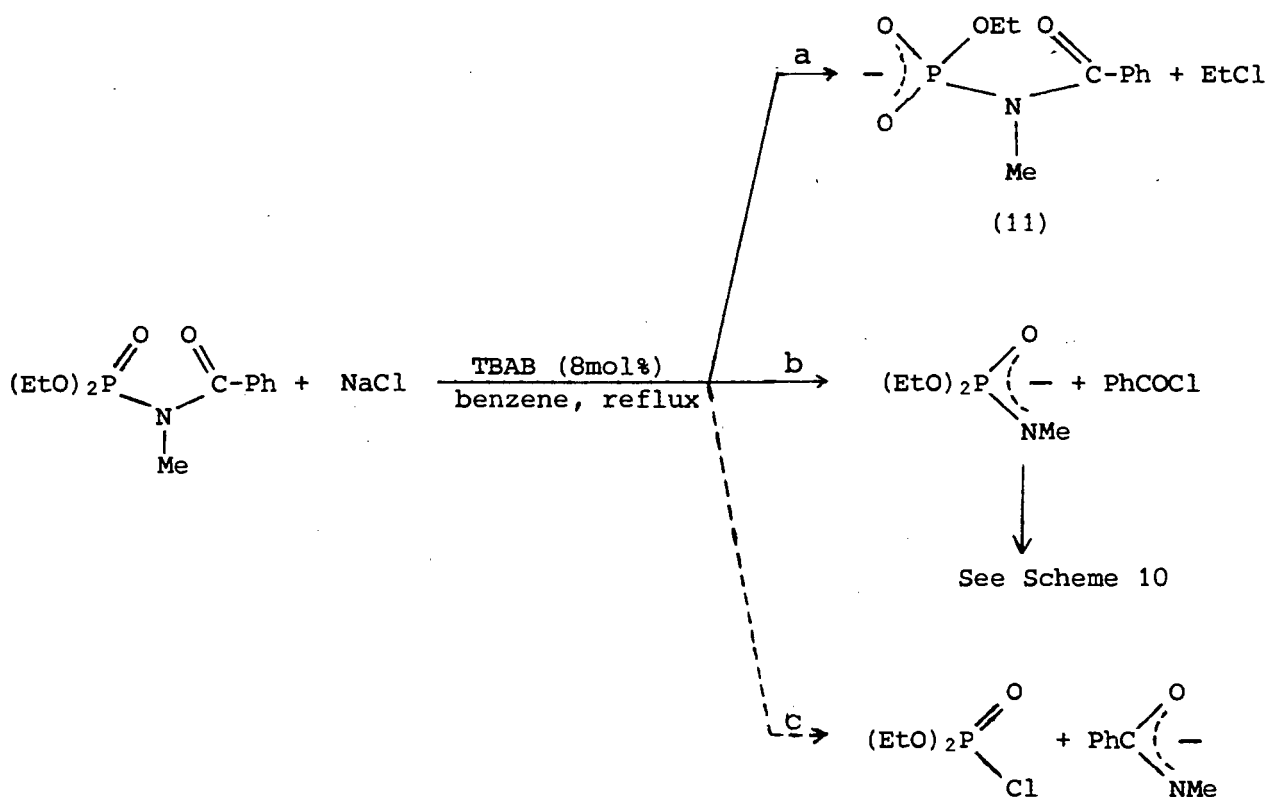
The formation of the products (IIIe), 4 and 6 are all accompanied by liberation of chloride ion which can then in turn, react with (IIIe) as outlined in Scheme 11.

The phase-transfer-catalysed reaction of (IIIe) with dry, finely powdered NaCl, in the presence of NaH was carried out in refluxing benzene. Although the reaction is extremely slow, prolonged heating results in the gradual increase in the concentration of the carboxamide (5). This is followed by the formation of the imide (6) and the simultaneous appearance of $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$ and ethylbenzoate (4) in low concentration. However, the most noticeable feature of this reaction is the deficiency of ethyl groups. The ^1H NMR integration ratio indicates about a 70% loss, suggesting extensive de-ethylation under the given reaction conditions. The attack of chloride ion at an ester carbon of (IIIe) (Scheme 13, pathway a), liberates ethyl chloride and the mixed imide monoanion (11). We were able to prove conclusively that de-ethylation was indeed occurring via liberation of ethyl chloride by conducting the following experiment. The benzoylation of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ with benzoyl chloride was repeated exactly as before. The apparatus was set-up to collect escaping gases in a trap containing CD_2Cl_2 cooled in a dry-ice acetone bath. The ^1H NMR spectrum of the CD_2Cl_2 solution recorded at -50°C at different intervals, showed clearly that ethyl chloride was being liberated ($\delta 1.50$, 3H, t, $J_{\text{H,H}}=8\text{Hz}$, $\delta 3.64$, 2H, q, $J_{\text{H,H}}=8\text{Hz}$).

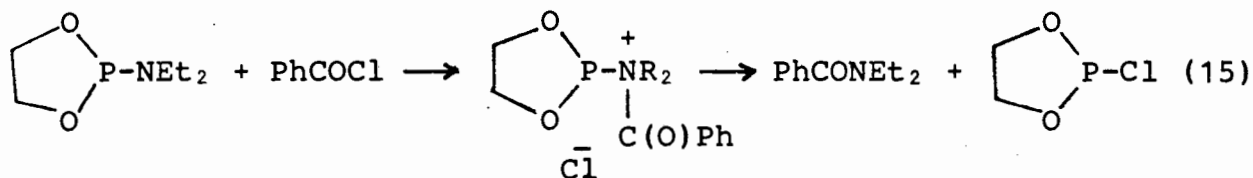
Attack at the carbonyl centre (Scheme 13, pathway b) yields benzoyl chloride and $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$ which are then capable of reacting as previously discussed (Scheme 10) to yield the remaining products observed in the reaction mixture. The attack of chloride ion at the carbonyl centre of (IIIe), reproducing the pair of substrates present in Scheme 10, thus proves that the base-catalysed N-benzoylation of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ is a reversible reaction.

Although the outcome of the phase-transfer-catalysed reaction of (IIIe) with chloride ion closely parallels that represented in Scheme 10, these observations still do not yield any additional information regarding the mechanism of the N-methyl transfer reaction.

Scheme 13



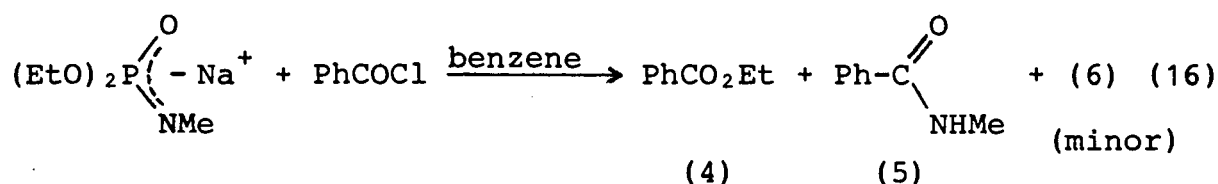
The attack of the chloride ion represented in Scheme 13 pathway (a) and (b) above, accounts well for the observed products, yet it is impossible to exclude the partial participation of attack by chloride ion at the phosphoryl centre. The orientation, represented in Scheme 13 as a tentative pathway (c), would result in the formation of (5) and diethylphosphorochloridate. The pathway (c), if present, would parallel the reported²⁹ selectivity of collapse of the quaternized product of the reaction of benzoyl chloride with cyclic P^{III} phosphoramidates (equation 15).



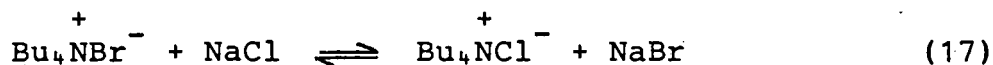
2.4.3 The Role of the Phase-Transfer Catalyst

The outcome of the reaction shown in Scheme 13 illustrates the significance of the reaction of the mixed-imide (IIIe) with the halide anion in the decomposition of the former. It was thus necessary to investigate the role of the 8 mol % bromide ion present in the reaction medium in the form of the catalyst, tetrabutylammonium bromide. The reaction of (EtO)₂P(O)NNaMe with benzoyl chloride in benzene in the absence of TBAB, was conducted. The results of this reaction parallel those of the reaction outlined in Scheme 10 with respect to the formation of the products (4), (5) and (6). However, in contrast to the phase-transfer-catalysed reaction, the uncatalysed reaction shows no trace of the mixed-imide (IIIe)

at any stage of the reaction, not even after 0.5 h at room temperature. It appears then that under these conditions, the reaction proceeds instead via a smooth transfer to the major products (4) and (5). The imide (6) is present only in minor concentrations (equation 16).



Further control experiments conducted in benzene under reflux have revealed that (IIIe) does not react at all with finely-powdered NaCl in the absence of TBAB, not even after a prolonged period (> 70 h) of heating. TBAB presumably serves to liberate the chloride ion from NaCl according to the equilibrium (17) and thus enhances its nucleophilicity.



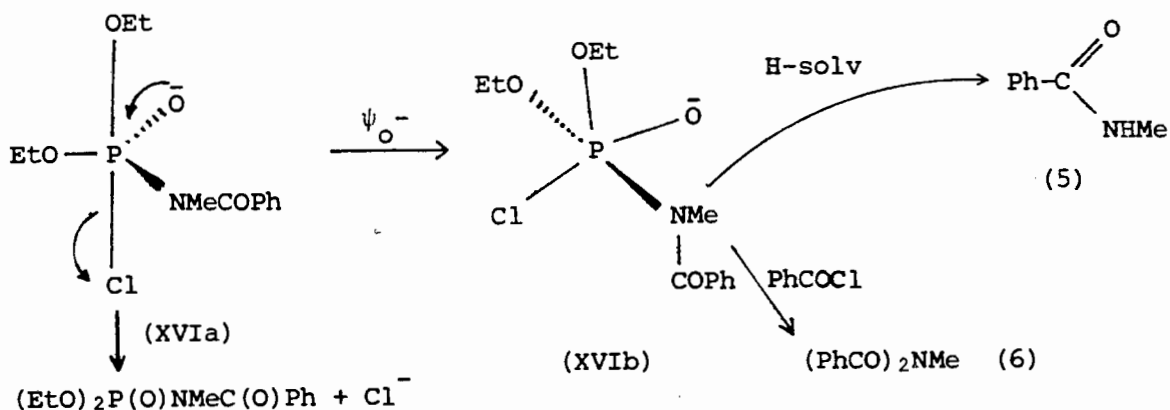
Tetrabutylammonium hydrosulphate was found to be unsuitable for this purpose as it does not catalyse the reaction of (IIIe) with NaCl.

However, it has been found that the reaction of (IIIe) with a stoichiometric amount of TBAB in the absence of NaCl does not lead to the formation of the carboxamide (5), but is accompanied by a degree of de-ethylation. When one compares the amount of TBAB present (8 mol %) in the reactions outlined in Schemes 10 and 13, with the extent of de-ethylation of (IIIe) in these reactions, it is logical that the ethyl groups

are lost as ethyl chloride as previously discussed, rather than as ethyl bromide. Loss of ethyl bromide probably contributes insignificantly to the overall de-ethylation process.

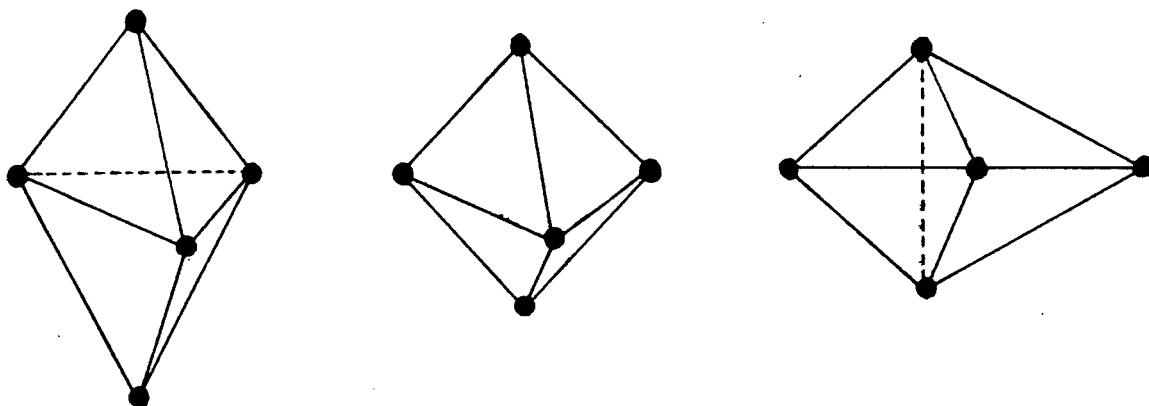
On the basis of the observed reactivity of (IIIe) towards halide ion in benzene, it is apparent that nucleophilic attack occurs predominantly at the ester and the carbonyl carbon atoms. It thus seems unlikely that direct attack of the halide ion at the phosphorus atom of (IIIe) is responsible for the N-methyl transfer reaction leading to the formation of (5) and (6) as proposed by Edmundson and Moran¹³ in Scheme 14.

Scheme 14



Although this mechanism accounts well for the products (5) and (6), we believe that it is not plausible for a number of reasons. Firstly, we have already illustrated the reluctance of nucleophiles to attack at the phosphoryl centre under these reactions conditions (equations 12 and 13). Secondly, it is well established that groups departing from P^{V} oxyphosphorane intermediates such as (XVIa) do so from the apical position. If these groups are not already in this position, once the intermediate is formed, they migrate there by the process of pseudorotation (ψ) about one of the equatorial

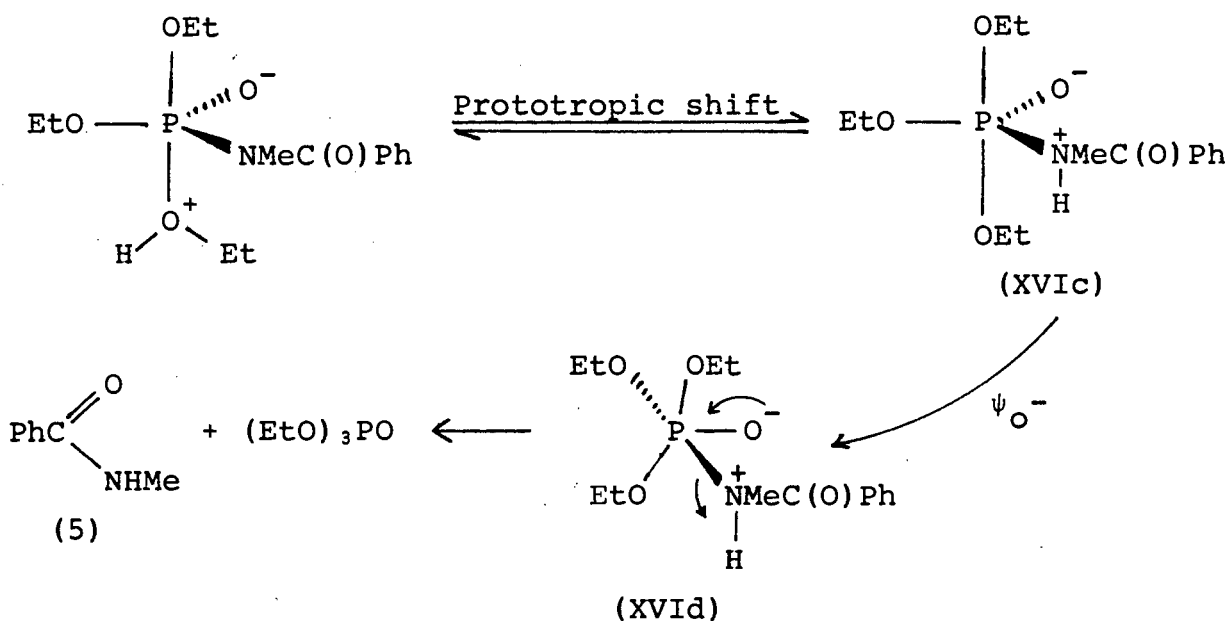
bonds. Pseudorotation for compounds of pentacovalent elements is defined³⁰ as the intramolecular process whereby a trigonal-bipyramidal molecule is transformed by deforming bond angles in such a way that it appears to have rotated by 90° about one of the interatomic bonds. Thus, in the diagram below, the substituent that is towards the viewer remains fixed, while the apical substituents are pushed backward and the equatorial substituents pulled forward as to produce a tetragonal pyramid intermediate where the fixed substituent is at the apex.



A continuation of this process leads to the second trigonal bipyramid, which appears to have been produced by rotating the first about the bond from the fixed substituent (the "pivot") to the central atom. This transformation is governed by a number of factors e.g. the electronegativity and the steric bulk of the migrating group. Generally larger groups remain in the equatorial position due to a lower spatial requirement in this position, while more electronegative groups are located preferentially at the apical position. As these are the longer more labile bonds, their electronic requirements are more readily fulfilled. The mechanism

proposed for P-N cleavage in Scheme 14 does not adhere to either of these general rules. The pseudorotation of the initially formed P^V intermediate (XVIa) in which the weakly apicophilic N-methylbenzamido ligand is in the equatorial position, in such a way as to locate this group in the apical position (XVIb), would be energetically unfavourable. Hence, we conclude that the formation of product (5) cannot be explained in terms of direct attack by chloride ion at phosphorus. In the case of hydroxylic nucleophiles (e.g. water and alcohols)⁸ however, attack occurs exclusively at the phosphoryl centre and this mechanism can be readily invoked in a suitable explanation for the formation of products resulting from P-N cleavage. The reaction of (IIIe) with ethoxide ion in excess ethanol yields in addition to the two products observed in the absence of ethanol (equation 13) the carboxamide (5), which results from attack of EtOH at phosphorus, Scheme 15.

Scheme 15

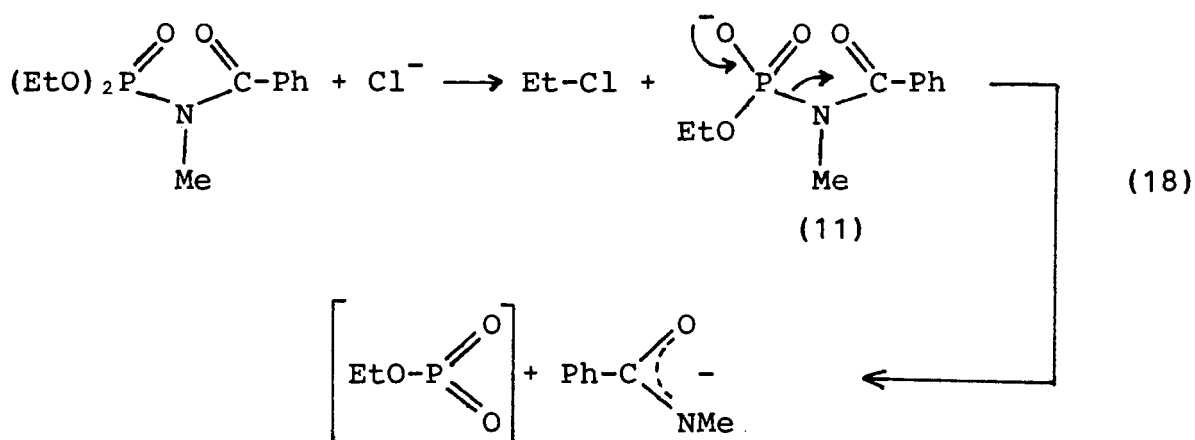


The positive charge acquired by the N-methylbenzamido group, leads to an increase in the electronegativity of this group and thus a lowering of the activation energy required for the pseudorotation involved in the transformation from (XVIc) to (XVIId) in Scheme 15.

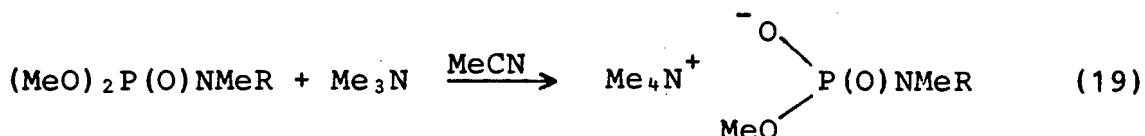
The mechanism proposed for ethanolysis of (IIIe) is the same as that for hydrolysis of (IIIe) under neutral conditions.⁸

2.4.4 The Role of the Monoanion 11

In view of the significant contribution of de-ethylation to both the benzoylation reactions of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ and the reaction of (IIIe) with halide ion, the possibility of the involvement of this reaction in the N-methyl transfer process was investigated. The rationale behind this investigation is illustrated in equation 18. The negative charge on the oxygen in 11 provides an "internal push" at the phosphoryl centre which results in a unimolecular P-N cleavage reaction.

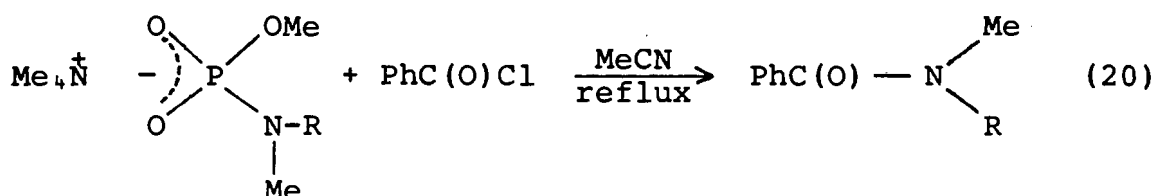


The tetramethylammonium salts of model monoanions were prepared independently from the reaction of $(\text{MeO})_2\text{P}(\text{O})\text{NMeR}$ with trimethylamine in acetonitrile according to equation 19.



- 12 a) $\text{R} = \text{COMe}$
b) $\text{R} = \text{Me}$

Preliminary results of the reactivity of these salts with benzoyl chloride in acetonitrile have revealed a facile quantitative conversion of 12a,b to the corresponding N-substituted benzamide derivatives 13a,b respectively, equation 20.

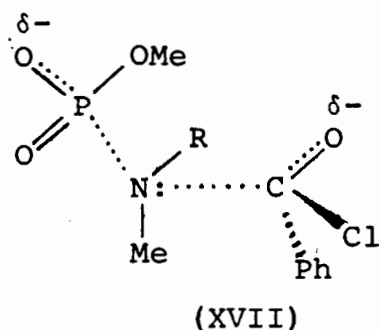


- 12 a) $\text{R} = \text{COMe}$
b) $\text{R} = \text{Me}$

- 13 a) $\text{R} = \text{COMe}$
b) $\text{R} = \text{Me}$

However, we have found that in the absence of benzoyl chloride, no P-N cleavage of the monoanions can be detected. This observation implies that the collapse of (12) via P-N cleavage requires electrophilic assistance by the benzoylating agent. The results are reminiscent of those discussed earlier for the formation of ethylbenzoate (equation 8, structure XI) and it appears that the conversion of (12) \rightarrow (13) is analogous to the conversion of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ to (4). It is worthwhile to point out that the reactions shown in equation 20 yield no trace whatsoever of the ester PhCO_2Me that would have arisen via an

electrophilically assisted P-OMe cleavage rather than the P-N bond cleavage reaction of (12). This constitutes a major difference in the behaviour of the anions (12) and $(\text{EtO})_2\text{P}(\text{O})\bar{\text{N}}\text{Me}$ in the presence of benzoyl chloride. However, the observed intramolecular selectivity of the monoanion (12) to collapse via P-N cleavage as opposed to P-O cleavage is consistent with the proposed mechanism for this type of reaction which proceeds via a transition state, structure (XVII).



If electrophilic assistance indeed is necessary for the transfer of the functional group from the phosphorus to the carbonyl carbon, it follows that the course of the reaction should be determined by the energy changes accompanying the processes of bond formation and bond cleavage, and not by the relative stability of the "free" anions RMeN^- and MeO^- . Now the P-O bond is 26 kcal mol^{-1} stronger than the P-N bond, it is not entirely surprising that the selectivity of collapse of (12) is observed. On the basis of the results given in equation 20, we conclude that the monoanion formed by de-ethylation of (IIIe), is capable of reacting with benzoyl chloride to yield the imide (6), thus offering an additional route (i.e. besides the base-catalysed benzoylation of the carboxamide (5) to this product. However, the de-ethylation of (IIIe) does not account for the formation of the carboxamide product (5). This conclusion

is consistent with the observation that under certain reaction conditions, the appearance of significant quantities of (5) in the product mixture is not accompanied by any detectable concomittant dealkylation. For example, it was found that in the uncatalysed benzylation of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ in benzene, the rapid (0.5 h) formation of (5) (50%) preceeds any detectable loss of ethyl groups. In addition, this conclusion that de-ethylation does not play a role in the nitrogen group transfer reaction is in accordance with the observation that benzylation of phosphinamidate anions $\text{R}_2\text{P}(\text{O})\text{NR}$ (R = alkyl, aryl), similarly result in the formation of the corresponding nitrogen-group-transfer products i.e. PhCONHR and $(\text{PhCO})_2\text{NMe}$. In these anions, the de-alkylation reaction is not possible because of the absence of ester groups.

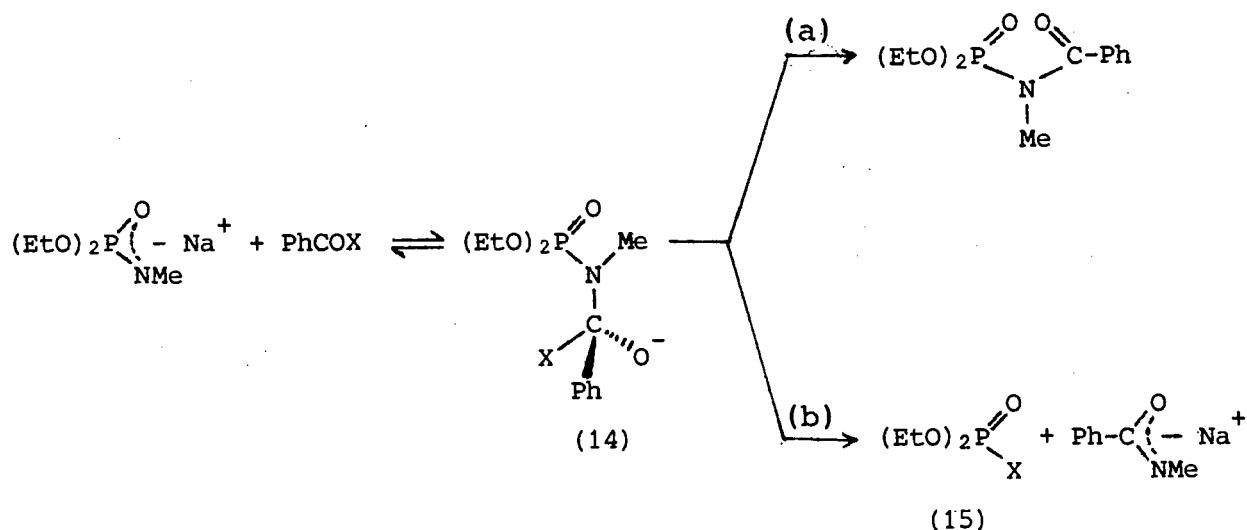
2.4.5 Proposed Mechanism of nitrogen group transfer

The results of the reactions discussed thus far, indicate that the decomposition of (IIIe) necessarily involves the attack of chloride at the phosphoryl centre. However, this attack is not direct and does not lead to the formation of a P^{V} trigonal bipyramidal intermediate which then collapses to products after pseudorotation in the manner previously described.

Nucleophilic attack by the N-methyldiethylphosphoramidate anion at the carbonyl centre of benzoyl chloride, results in the formation of a typical tetrahedral intermediate (14) which can then collapse via two distinct pathways. The expulsion of X ($\text{X} = \text{Cl}$) from (14) gives rise to the expected product, the mixed imide (IIIe) (Scheme 16, pathway (a)). Alternatively,

(14) may collapse via an intramolecular transfer of X from the tetrahedral carbon atom to the phosphoryl centre, resulting in P-N cleavage and the expulsion of the conjugate base of N-methylbenzamide (Scheme 16, pathway b). The transfer of X and the resultant P-N cleavage in all probability occurs as one concerted step.

Scheme 16



The reaction proceeding via pathway (b) provides a means of accounting for the N-methyl transfer process.

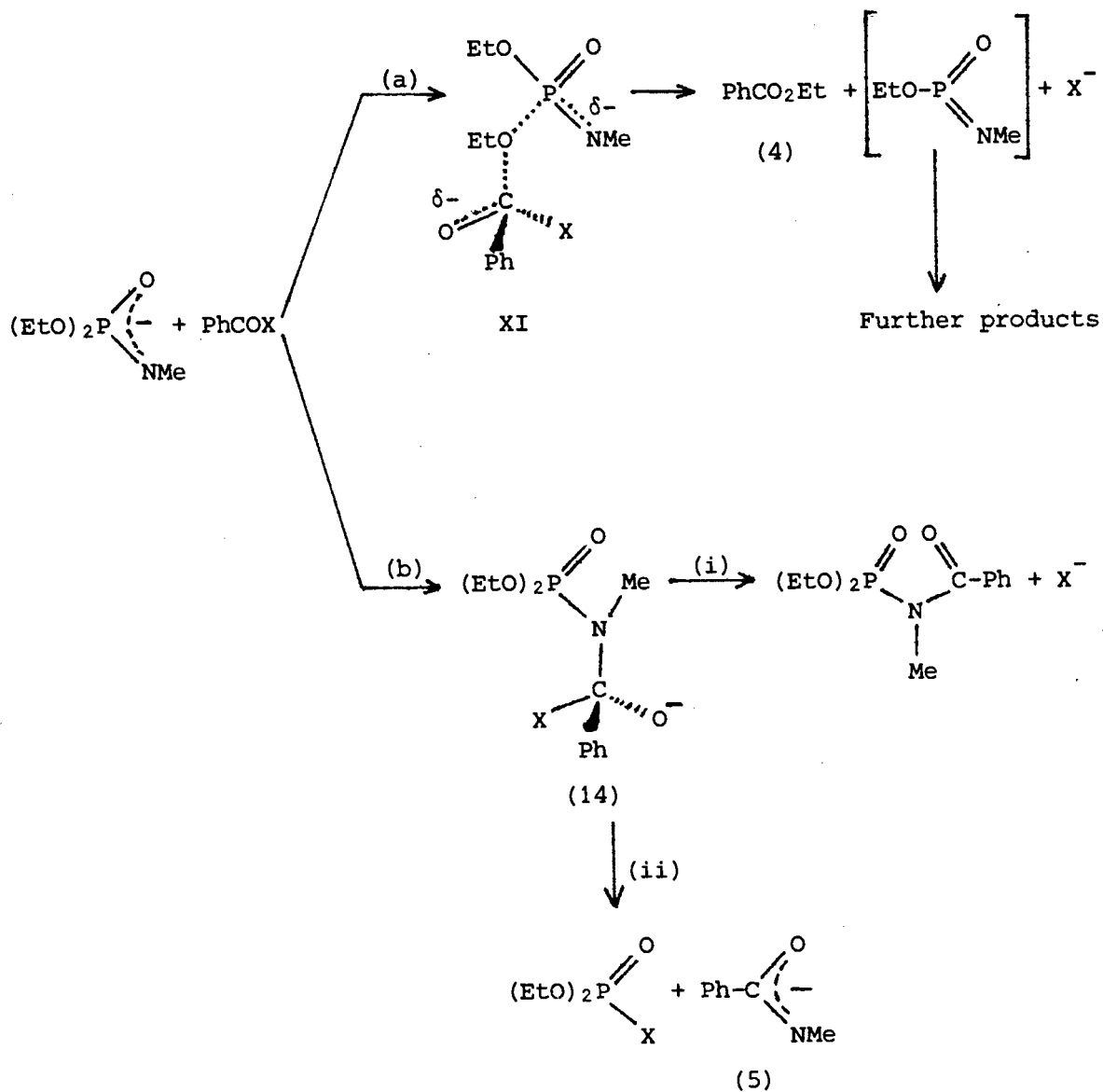
This implication prompted the investigation aimed at establishing in more detail, the effect of the group X in the benzoylating agent PhCOX on its reaction with the sodium salt of N-methyldiethylphosphoramidate.

We determined the products of the uncatalysed reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$ with benzoyl fluoride, chloride and bromide. For the series of PhCOX ; $\text{X} = \text{F}, \text{Cl}, \text{Br}$, the nature of the products remains unchanged (i.e. the ester (4) and amide (5) are the major products while imide (6) remains the minor

product). However, we do find that the relative concentrations of (4) and (5) vary with the nature of X (X = F, Cl, Br).

The overall reaction is best summarized in the Scheme 17, below.

Scheme 17



The observed increase in ester formation and the relative decrease in the N-methyl transfer is tabulated below, table (2).

Table (2)

X	% Conc. of (4)	% Conc. of (5)
F	21	79
Cl	38	62
Br	53	47

The changes in the electrophilicity of the carbonyl centre of the benzoylating agent PhCOX , due to the differences in the electronegativity of the halogens F, Cl, and Br, exerts a parallel influence on pathway (a) and (b) and is thus not expected to affect the relative concentrations of (4) and (5). However, the mechanism proposed for the formation of the benzoic ester is virtually a nucleophilic substitution of an acyl halide, and the usual order of reactivity in such a reaction is $\text{PhC(O)F} < \text{PhC(O)Cl} < \text{PhC(O)Br}$ ³¹ which is in excellent agreement with the observed order of increase in ester formation. The formation of (5) proceeds via the tetrahedral intermediate (14). If the collapse of (14) involves the intramolecular transfer of the halogen from carbon to phosphorus as proposed, the relative yield of the conjugate base of (5) should reflect the affinity of a halide for the phosphoryl centre. It is known³² that this affinity decreases in the order $\text{F} < \text{Cl} < \text{Br}$ which agrees with the observed trend in the N-methyl transfer reaction.

If the formation of (4) and (5) are irreversible (which is most likely the case), the relative concentrations reflect directly the relative rates of these two competing pathways. In such a case, the relative rates of ethoxide transfer versus N-methyl transfer (pathway (a) vs. (b)) vary in the order 3.7, 1.7, 0.7 for X = F, Cl, Br respectively.³³

Furthermore, we need to comment on the competitive collapse of (14) via either pathway (i) or (ii) with respect to X.

The absence of the mixed-imide (IIIe) in the final product mixtures of the benzoylation reactions involving benzoyl fluoride, chloride and bromide, implies that in refluxing benzene collapse of the intermediate (14) occurs exclusively via P-N cleavage (Scheme 17, pathway ii). However, at room temperature the alternative pathway of collapse, i.e. expulsion of X via pathway (i), does become apparent and although this is only to a minor extent if indeed at all, the exact extent to which it does occur is determined by the halide.

We have found that at room temperature, collapse of 14 occurs via:

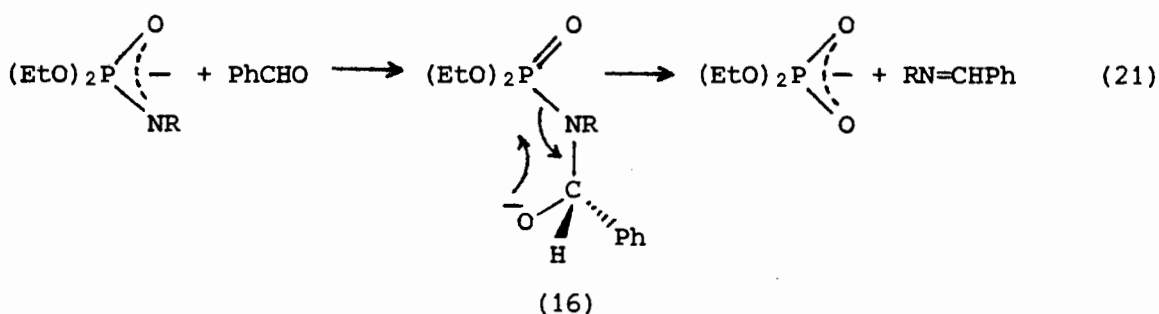
pathway (ii) for X=F

pathway (i) and (ii) for X=Cl ((ii) > (i))

pathway (i) for X=Br

These observations are in agreement with the increasing leaving abilities of the halide anions i.e. $\text{Br}^- > \text{Cl}^- > \text{F}^-$.³¹

Wadsworth and Emmons²⁰ have found that N-alkylphosphoramidate anions react with a variety of carbonyl and thiocarbonyl compounds (e.g. CO₂, CS₂, RR'CO) to yield the corresponding imine-type derivatives. It is claimed that these syntheses proceed stepwise through an adduct via a mechanism which is analogous to that operating in the Wittig-Horner⁶⁶ reaction. In a particular example which closely resembles the reaction presently under discussion, N-alkyldiethylphosphoramidate anion is allowed to react with benzaldehyde to give benzaldimines in good yield (equation 21). The collapse of the adduct (16) is based on the excellence of diethylphosphate as a leaving group.

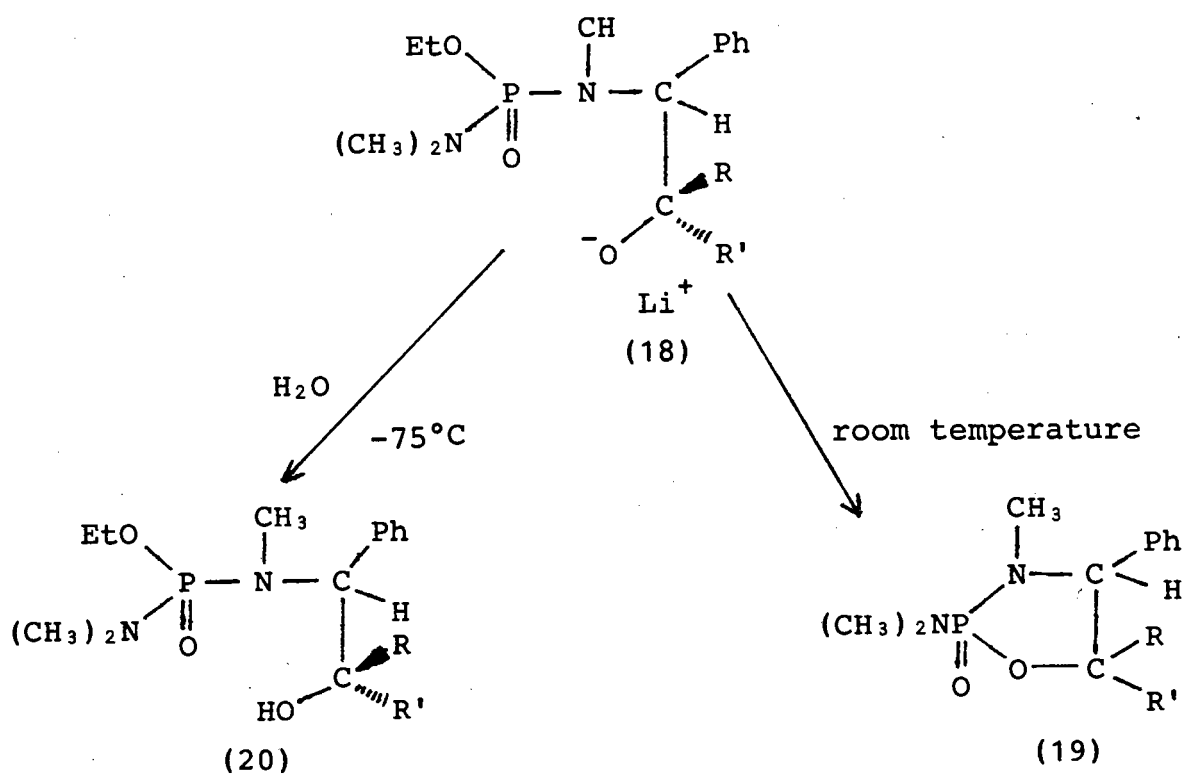
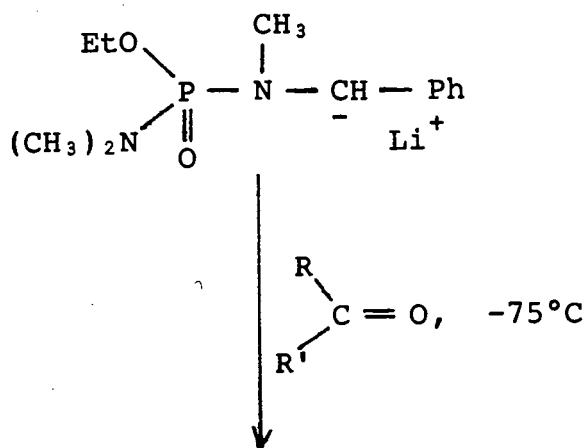
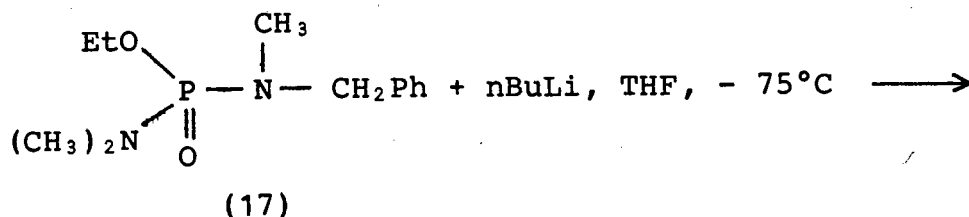


The collapse of (14) via the pathway (b) Scheme 16 that we propose is thus a modification of the Wadsworth-Emmons reaction, with the lability of the C-X bond and the favourable incipient carboxamide formation directing the intramolecular nucleophilic attack at phosphorus by X rather than by the oxyanion.

The results of the investigations by Savignac *et al*³⁴ into the reactivity of the phosphoramidate (17) with strong bases and the subsequent condensation of the carbanion thus formed with electrophiles such as aldehydes and ketones, lend further credibility to the proposed mechanism of the N-methyl transfer

reaction. It is suggested that the two products formed in this reaction arise from a related intermediate (18), the collapse of which is dependent upon the reaction temperature (Scheme 18).

Scheme 18

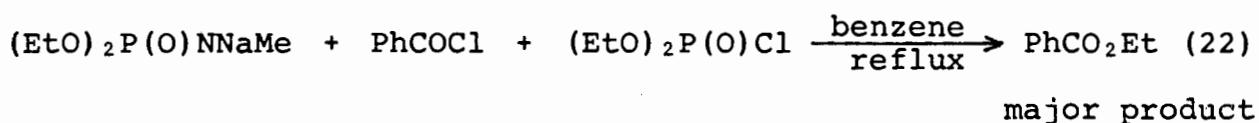


At room temperature (18) undergoes rapid cyclization via attack of the oxyanion at phosphorus with expulsion of ethoxide to yield (19). At low temperature however, (20) is formed via protonation of the oxyanion. These results further illustrate that the collapse of the kind of intermediate proposed by Wadsworth and Emmons is dependent on a number of factors. In particular, thermodynamic factors as seen in the above example, the excellence of the leaving group as Wadsworth and Emmons have suggested,²⁰ and the lability of the C-X bond as we have shown, also needs to be taken into account.

However, while the mechanism may offer an explanation for the N-methyl transfer process, it also introduces a reactive electrophile (15) into the reaction medium which is capable of further reacting with nucleophilic species present.

Independent experiments have shown that (15) (X=Cl) reacts with $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ according to equation 9 and with $\text{PhC}(\text{O})\text{NNaMe}$ according to Scheme 4. The absence of the distinctive N-Me triplet ($\delta 2.96$, t, $J_{\text{PNCH}} = 9.5$ Hz) characteristic of the amidophosphate (8), in the product mixtures of the various base catalyzed benzoylations of phosphoramidate anion that we have studied, is particularly conspicuous. In fact, it appears to argue against the formation of (15), and hence against the proposed mechanism of the N-methyl transfer reaction (Scheme 16, pathway b). It is conceivable that the absence of (8) in the product mixtures may be due to the participation of alternative reactions that preclude the interaction between $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ and (15) that is necessary to form (8).

Since interaction with benzoyl chloride is a major alternative available to $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$, we conducted a competitive experiment aimed at establishing the relative reactivities of benzoyl chloride and (15) ($\text{X}=\text{Cl}$) towards the anion. The reaction, involving equimolar amounts of the three substrates, was conducted in refluxing benzene in the absence of TBAB. The major product that is observed after heating for 17 h is ethylbenzoate (equation 22). This result shows that although (15) ($\text{X}=\text{Cl}$) is formed as a by-product in the benzoylation reaction, in the presence of the competitive electrophile benzoyl chloride, the latter precludes its reaction with the substrate anion.



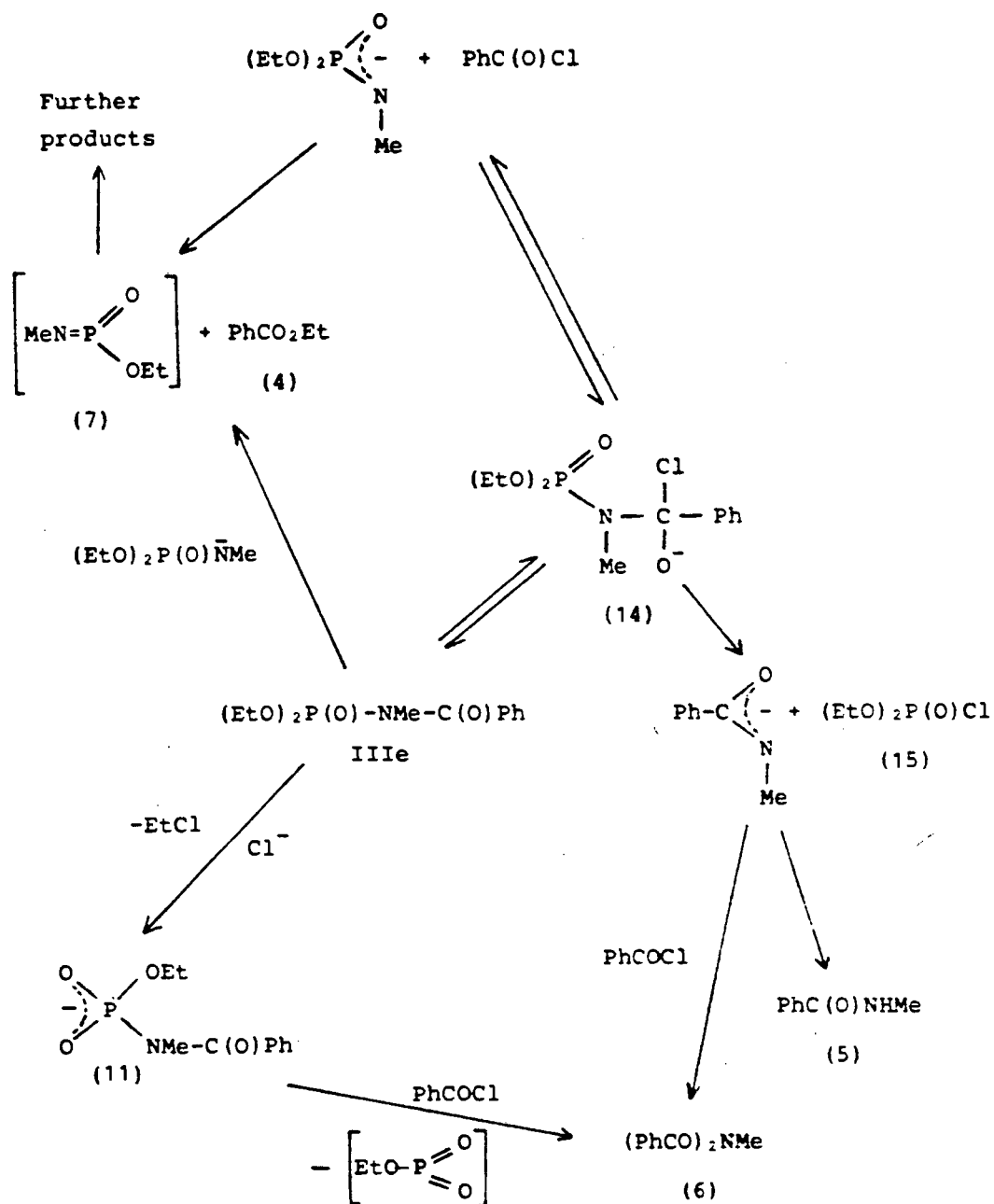
Unreacted phosphoramidate anion and N-methylbenzamide is present in lower concentration in the final product mixture. The outcome of the reaction thus largely parallels that of the uncatalysed benzoylation of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ conducted in benzene.

This result indicates that under these competitive reaction conditions, the phosphoramidate anion displays greater reactivity towards a carbonyl than towards a phosphoryl centre.

The diverse range of reactions that are associated with the base-catalysed benzoylation of N-methyldiethylphosphoramidate anion, are summarized in Scheme 19. As a result of the strong driving force away from a phosphoric amidoester substrate,

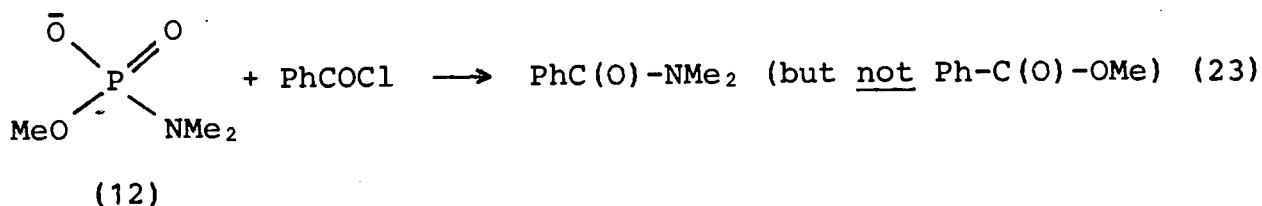
towards carboxylic amide and ester products, complex product mixtures are found to prevail under a variety of reaction conditions. We thus conclude that the benzylation of N-methyldiethylphosphoramidate anion is an unsatisfactory synthetic route to the corresponding tertiary N-benzoyl mixed-imide system.

Scheme 19



The re-examination of this reaction has nevertheless proved extremely fruitful in that it has opened-up new areas of research.

The observation that monoanions of phosphoric amidoesters (12) can aminate (but not alkoxylate) acyl chlorides to give amides (but not esters) according to equation 23, is surprising in the light of the stability of the methoxide and dimethylamide conjugate bases.



Since these reactions offer an insight into the nature of the phosphorylation process, which is fundamental to a number of biochemical systems, they are presently being investigated in more detail in our laboratory. Product studies of the reactions of the amidoester anions $(\text{RO})(\text{R}'_2\text{N})\text{PO}_2^-$ and acyl chlorides $\text{R}''\text{-C(O)-Cl}$, are being conducted in order to test the generality of this reaction. We are interested in attempting to reverse the process from amination to alkoxylation by varying the nature of the ester and amine groups in the substrate. The reaction will also be carried out in the presence of a reagent which would trap the metaphosphate species, and thus provide evidence for its participation.

CHAPTER 3

Reactions of mixed-imides with Grignard reagents

3.1 INTRODUCTION

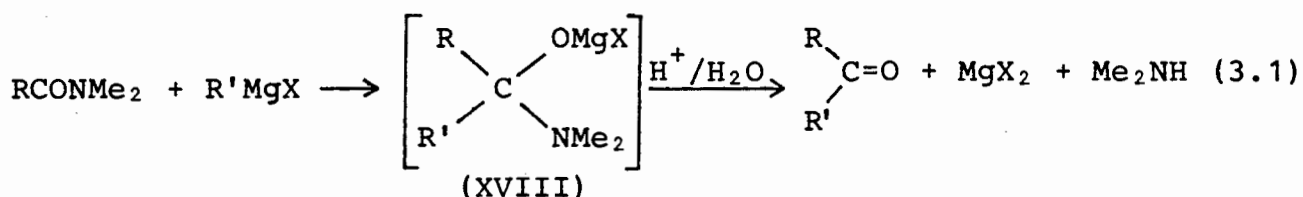
In attempting to establish the role of the mixed-imide (IIIe) in the formation of the major reaction products resulting from the benzoylation of phosphoramidate anions, additional insight into the reactivity of these compounds towards nucleophilic species has been gained.

In the presence of nucleophilic species, the mixed-imide (IIIe) collapses via either phosphorus-nitrogen cleavage or via carbon-nitrogen cleavage, depending upon the nature of the nucleophile. Hydroxylic nucleophiles (e.g. water and alcohols)⁸ attack exclusively at the phosphoryl centre, while anionic nucleophiles (e.g. alkoxide and halide anions) are selective towards the carbonyl and the ester carbon centres. In an attempt to include a wider range of nucleophiles in this generalization, the reactions of mixed-imides (III) towards carbon nucleophiles were studied. The main purpose of the investigation was to establish whether new phosphorus-carbon or new carbon-carbon bonds are formed in these reactions. Because of the relative ease with which they can be prepared, it was decided to use Grignard reagents as the precursors for the carbon nucleophiles in these reactions.

Although Grignard reagents have been extensively used in organic synthesis, their reactivity towards mixed-imides has not been previously reported in the literature. It is reasonable to suppose that there would be a degree of overlap between the chemistry of the mixed imides (III) and that of carboxylic acid amides and phosphoryl esters. For this reason we consider briefly the results reported in the literature of the reactions of

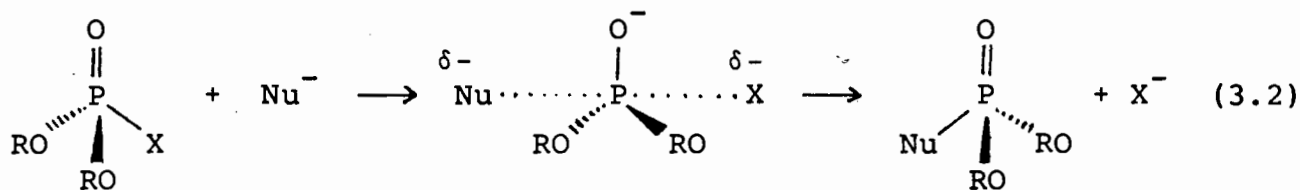
the latter two kinds of compounds with Grignard reagents.

Nucleophilic addition to the amide carbonyl function takes place with Grignard reagents. It is generally accepted that the reaction proceeds via the stable addition complex (XVIII), which on treatment with aqueous acid, produces a ketone or aldehyde (equation 3.1).³⁵



An examination of the observations made for the analogous reaction involving a variety of phosphorus esters, $(\text{RO})_2\text{P}(\text{O})\text{X}$,^{36, 37, 38} reveals that the outcome is much more complex than in the case of the amide.

The reaction of phosphoryl compounds with nucleophiles has been pictured as proceeding via a pentacovalent trigonal bipyramidal transition state³⁹ (equation 3.2) with inversion of configuration at the phosphoryl centre.⁴⁰

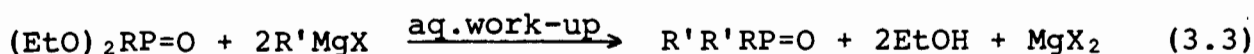


The direction and the rate of this reaction is determined by an interdependence of a number of different factors. Electron-withdrawing groups, for example, enhance the reaction by increasing the susceptibility of phosphorus to nucleophilic attack and by stabilising the transition state.³⁸ The strength

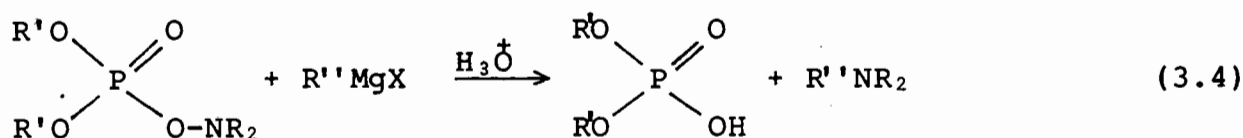
of the P=O bond also needs to be taken into account when considering attack at the phosphoryl centre. Groups which decrease the energy required to overcome the P-O $p\pi d\pi$ overlap in going from the ground state to the transition state, increases the rate of the reaction.³⁷

A variation in the nature of the group X in the phosphoryl ester $(RO)_2P(O)X$, greatly influences the outcome of its reactions with Grignard reagents as is illustrated in the following examples.

The reaction of diethylphosphonate (X = Alkyl, Aryl) with Grignard reagent is an acceptable synthesis for phosphine oxides (equation 3.3) The reaction proceeds with successive substitution of the ester groups according to the mechanism above.



The successful use of o-phosphoryl-N,N-dimethylhydroxylamines (X = -ONMe₂) as electrophilic amination reagents in the preparation of all kinds of tertiary amines,⁴¹ is based on the nucleophilic attack by the Grignard reagent at the nitrogen atom (equation 3.4).

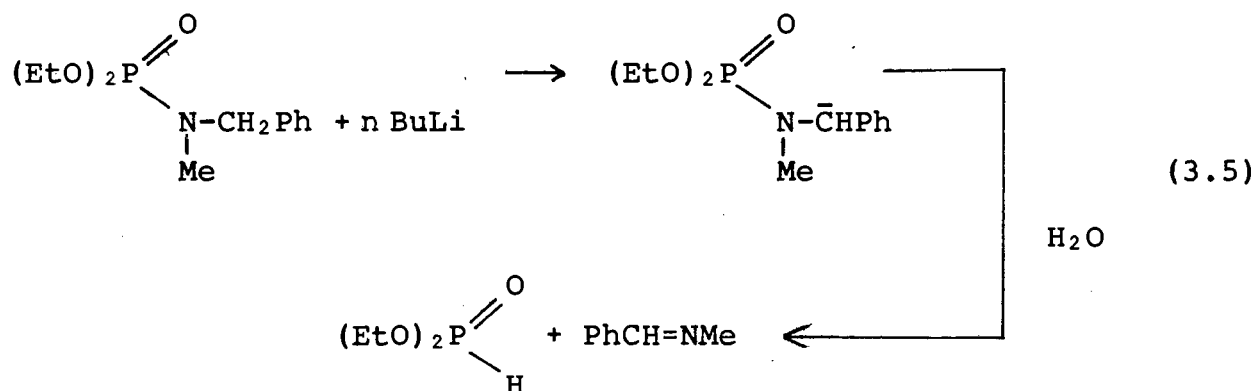


R' = alkyl, aryl

R = CH₃

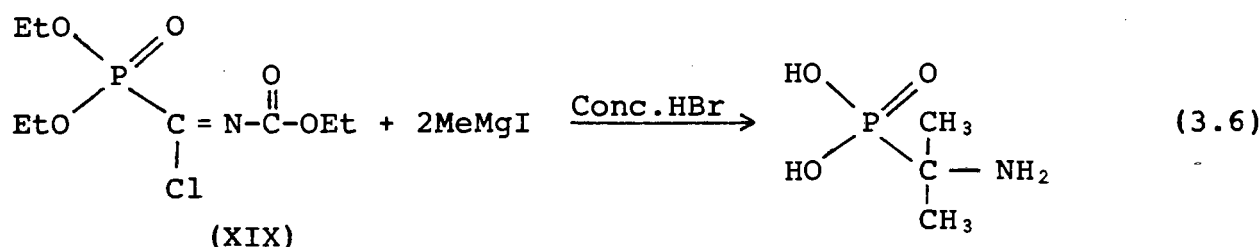
The authors do not mention whether or not they observe any o-phosphinyl-N,N-dimethylhydroxylamines which would result from

attack at phosphorus. The reaction of phosphoramidates with Grignard reagents are not discussed in the literature but the analogous reaction of N-methyl-N-benzyl-diethylphosphoramidate ($X = -N(CH_3)CH_2Ph$) with n-butyllithium is worth mentioning as it further illustrates a rather unexpected reaction of phosphorus esters with carbon nucleophiles,⁴² (equation 3.5).



Here the carbanion acts as a base to the weakly acidic methylene protons of the N-benzyl substituent.

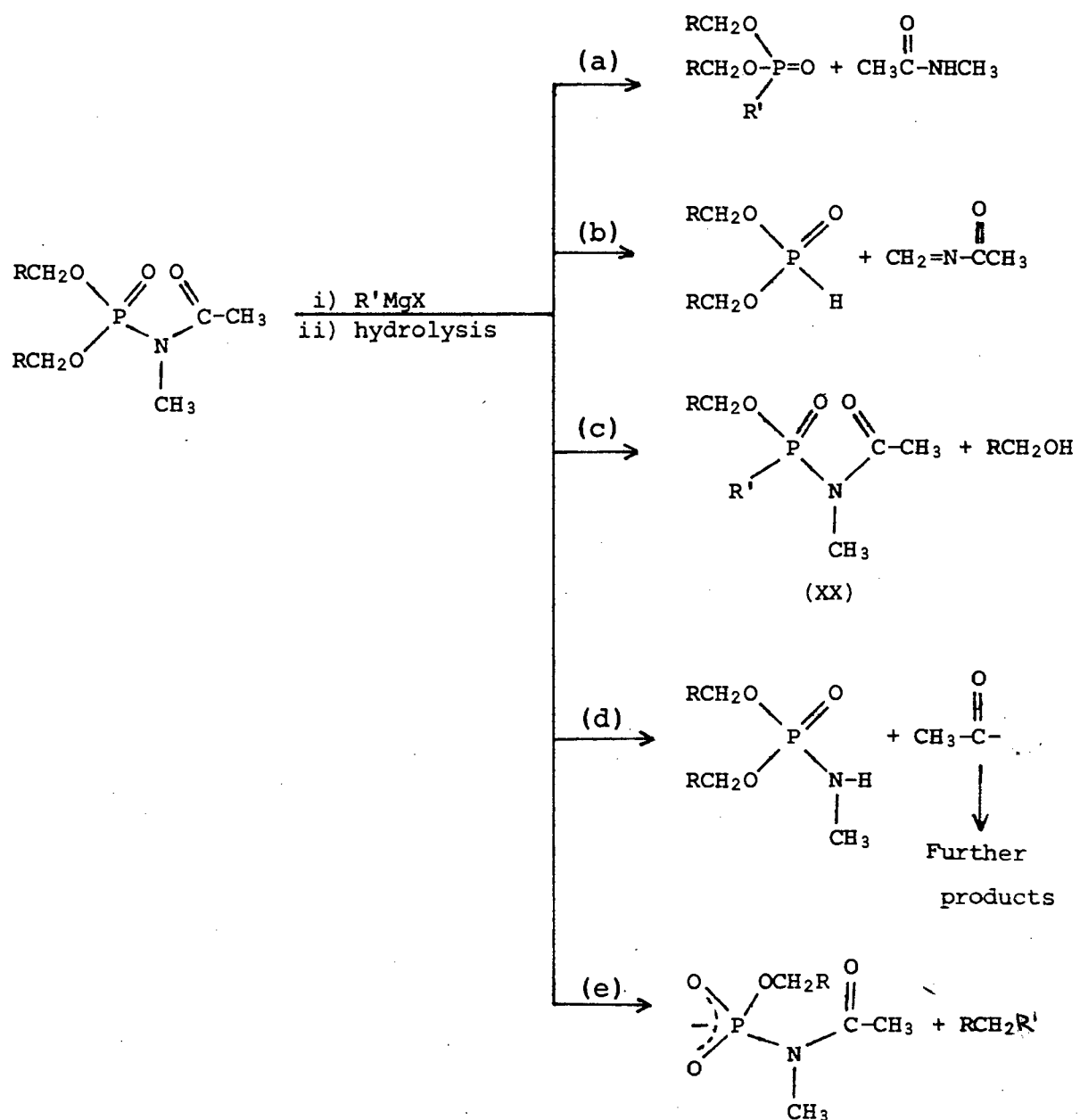
The reaction of O,O-diethyl-1-[N-ethoxycarbonylimino]-1-chloromethylphosphonate (XIX) with Grignard reagents⁴³ constitutes an important preparation of 1-aminoalkylphosphonic acid which is of interest because of biological importance and chelating properties (equation 3.6).



Although (XIX) contains both the phosphoryl and carbonyl electrophilic centres, the reaction proceeds via addition and substitution

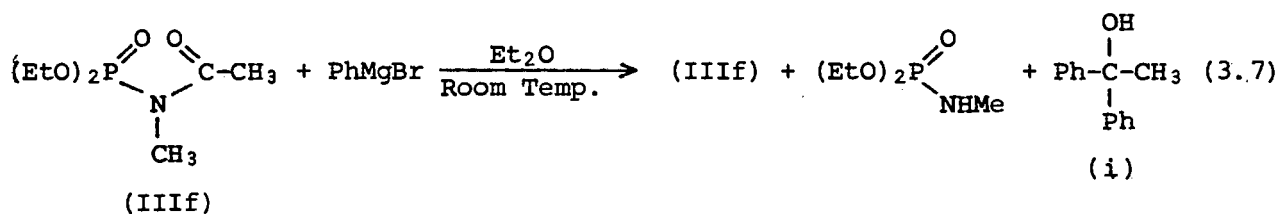
at the unsaturated carbon. These results serve to illustrate the great diversity of the reactions of phosphorus derivatives with Grignard reagents and makes it difficult to generalize as to the outcome of the reaction of (III) with Grignard reagents. However, they enable us to propose the following general scheme of the pathways along which this reaction can proceed.

Scheme 20



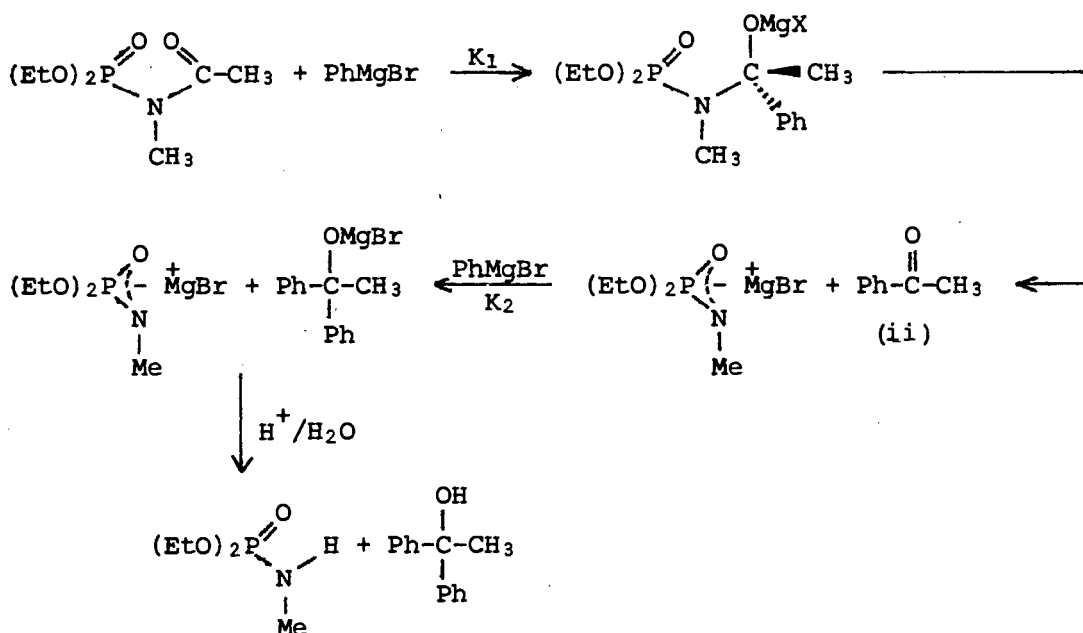
3.2 RESULTS AND DISCUSSION

The reaction between equimolar portions of phenylmagnesium bromide and N-methyl-N-acetyldiethylphosphoramidate(IIIIf) was conducted in dry ether at room temperature. The reaction is highly exothermic and is complete very soon after the addition of (IIIIf) to the phenylmagnesium bromide solution. The outcome of the reaction is summarized in equation 3.7 below.



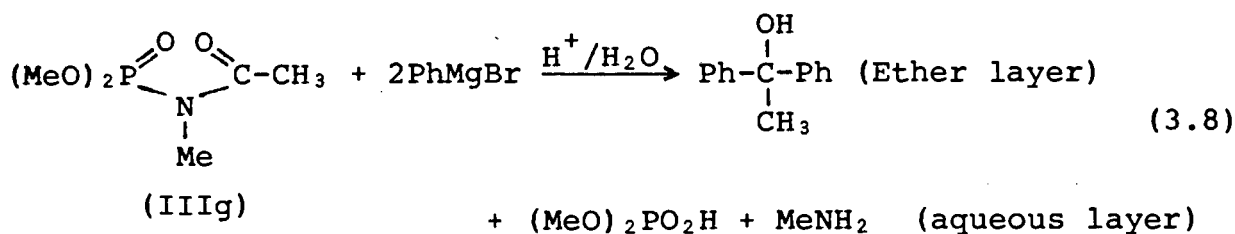
Analysis of the ethereal layer by ^1H NMR after aqueous acidic work-up revealed that the reaction proceeded entirely with attack by the carbanion (C_6H_5^-) at the carbonyl centre of (III_f) (Scheme 16, pathway (d)). Diphenylmethyl carbinol (i) was identified from the elemental analysis and its ^1H NMR spectrum (CDCl_3), particularly its $-\text{CH}_3$ resonance, $\delta 2.73$ (s, 3H). The three products indicated in equation (3.7) were isolated by column chromatography using a 10% ethyl acetate-chloroform mixture as eluting solvent. The observation that the relative concentrations of the products are in the ratio 1:1:1 supports the proposed Scheme 21, outlining their formation.

Scheme 21

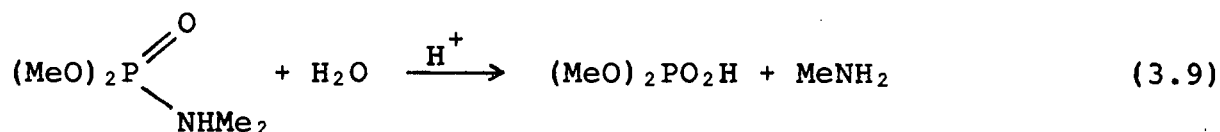


The absence of acetophenone (ii) from the product mixture implies that rate constant $K_1 \ll K_2$ which is in agreement with the greater electrophilicity of the carbonyl centre in acetophenone than that in (IIIIf). As a result, any acetophenone formed reacts immediately with the excess Grignard reagent to give the carbinol (i). This accounts for the unreacted (IIIIf) present in the final product mixture.

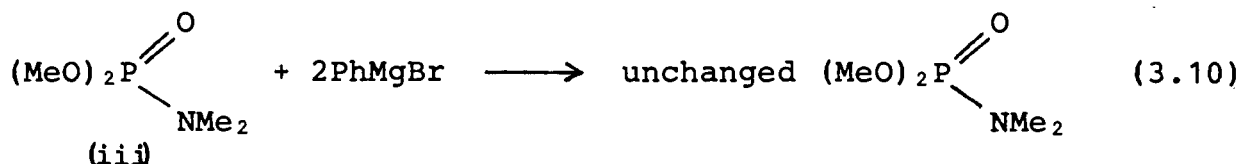
In an attempt to promote attack at the phosphoryl centre, the concentration of phenylmagnesium bromide was doubled in its reaction with N-methyl-N-acetyldimethylphosphoramidate (IIIg). However, there is no difference in the pathway of this reaction from that proposed previously (Scheme 21) and (IIIg) collapses completely via attack at the carbonyl centre (equation 3.8).



Only the carbinol product remains in the ethereal layer as the phosphoramidate is hydrolysed to the water-soluble acid during aqueous acid work-up (equation 3.9).



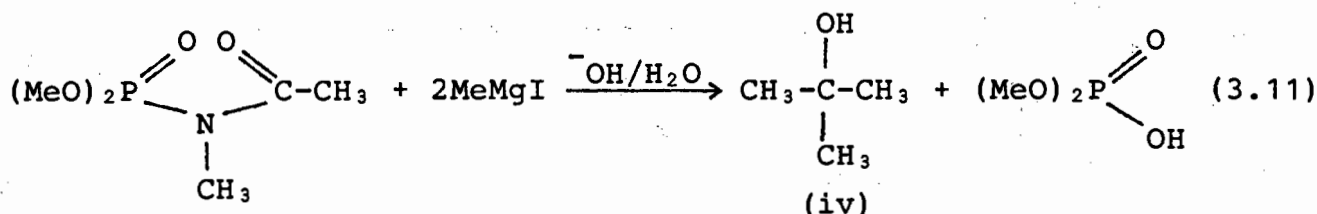
That the direction of bond cleavage in (IIIIf) and (IIIg) is not as a result of the competitive electrophilicity of the phosphoryl and carbonyl centres, was confirmed by the outcome of this same reaction involving N,N-dimethyldimethylphosphoramidate (iii) (equation 3.10).



The substrate (iii) remains largely intact after the addition of phenylmagnesium bromide. However, thin-layer chromatography does indicate the presence of a minor product in the ethereal layer. This product which could not be isolated, is also present to a minor extent in the ethereal layer of reactions outlined in equations (3.7) and (3.8). Although we are not certain as to its identity, we believe that its presence is related to proton resonances in the regions of $\delta 1.3$ and $\delta 4.8$ in the ^1H NMR spectra of these mixtures.

Berlin and Pagilagan⁴⁴ have shown that ethyldiphenylphosphinate and different Grignard reagents react at different rates dependent upon the size of the organic part of the Grignard

reagent. We have found that steric factors do not predominate in these reactions of (IIIIf) and (IIIg) and the reluctance of the carbanion to attack at the phosphoryl centre is evident even in their reaction with methylmagnesium iodide (equation 3.11).



Because of the considerable water solubility of t-butanol (iv) as well as its volatility (b.p. 80-82°C), the ethereal layer is almost entirely devoid of products after aqueous alkaline work-up. The phosphoramidate accompanying the formation of t-butanol is hydrolyzed to the corresponding acid during alkaline work-up.⁴⁵ A more detailed understanding of this reaction was gained when it was repeated on a larger scale, without subsequent aqueous work-up. After the reaction was completed, the product mixture was simply stirred in an open flask and the products allowed to hydrolyze by exposure to atmospheric moisture. The white precipitate obtained after spontaneous evaporation of the ether was digested in chloroform. It is clear from the ¹H NMR spectrum (Figure 3) of the supernatant chloroform extract, that although attack by the methyl carbanion occurs predominantly at the carbonyl centre, a number of the other pathways outlined in Scheme 20 are involved in this reaction to a minor extent. In addition to the expected products t-butanol and N-methyldimethylphosphoramidate, the spectrum indicates that N-methylacetamide, methanol and acetone are also

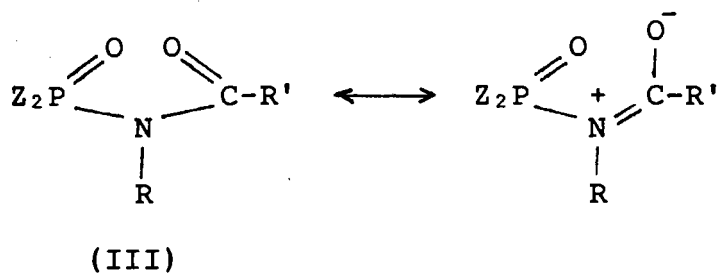
formed in low concentration. The presence of methanol and acetone was tentatively confirmed by spiking the ^1H NMR sample with authentic samples of these compounds.

If N-methylacetamide is indeed formed by attack of the methylcarbanion at the phosphoryl centre, it should be accompanied by the formation of dimethylmethylphosphonate $(\text{MeO})_2\text{MeP}(\text{O})$, (Scheme 20, pathway (a)). However as the latter compound is not detectable in the spectrum of the final product mixture, the possibility that N-methylacetamide is in fact formed via hydrolysis of the unreacted mixed-imide, cannot be ignored.

The presence of methanol can only tentatively be attributed to the minor involvement of methoxide expulsion according to Scheme 20 pathway (c). The N-acetylphosphoramidate (XX) expected to accompany its formation, was not identified in the ^1H NMR spectrum, possibly due to its low concentration and signal overlap. In the light of the participation of these alternative pathways in the reaction, the stoichiometry of the reaction is such that there is not sufficient methylmagnesium iodide to complete the conversion of acetone to t-butanol and its presence is, in fact, supportive of the mechanism proposed in Scheme 21.

In conclusion, phosphoric-carboxylic imides (III) can act as both phosphorylating and acylating reagents of nucleophiles. Under neutral conditions, hydroxylic nucleophiles (e.g. water and alcohols)⁸ attack exclusively at the phosphoryl centre. This regiospecificity results from the retained "carboxamide resonance" effect in (III) which is responsible for the

electrophilic character of the phosphorus atom.



The reluctance of anionic nucleophiles (alkoxides, halides and carbanions) to attack at the phosphorus can be understood in terms of the high energy requirements for pseudo-rotation to occur in the oxyphosphorane which is an intermediate formed (as previously discussed) in this reaction (section 2.4.3).

CHAPTER 4

Experimental

4.1 GENERAL

Benzene and toluene used as reaction media were distilled over metallic sodium and stored over sodium wire. Diethyl ether was distilled as required and stored over molecular sieves (4Å). Other solvents were purified in the conventional manner. Aluminium-backed silica gel plates (Merck, Kieselgel-60F₂₅₄, Art. 554) were used for thin-layer chromatography (TLC). Column chromatography was carried out on silica gel columns (Merck, Kieselgel 40, Art. 10180, 70-230 mesh ASTM). In both cases, an ethyl-acetate-chloroform (1:4) mixture was used as eluting solvent, unless otherwise stated.

The ¹H NMR spectra were recorded on a 60 MHz Varian EM360 and a 100 MHz Varian XL100 spectrometer with tetramethyl silane (TMS) as internal reference. Mass spectra were recorded on a V₆ Micromass 16F Spectrometer operating on an ion source temperature of 200°C. Melting points were recorded on a Fisher-Johns m.p. apparatus. Solvents were removed under reduced pressure using a Büchi rotary evaporator, equipped with a Kotterman water bath. All precautions were taken to ensure complete anhydrous conditions in all reactions.

All analyses for C, H and N were carried out at the University of Cape Town by Mr. W.R.T. Hemsted.

4.2 PREPARATION OF SUBSTRATES

Benzoyl chloride (Merck) was distilled before use.

Benzoyl Fluoride.⁵⁰

20 mmol of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-Crown-6) was dissolved in 50 cm³ of dry benzene and 0.2 mol of potassium fluoride was added. After the heterogenous system had been stirred for about 0.5 h, 0.1 mol of benzoyl chloride was added and the resulting mixture was allowed to stir for a further 2 h. Benzoyl fluoride was collected by distillation. Yield 60%, b.p. 156-157°C. Lit.⁵¹ b.p. 157-159°C.

Benzoyl Bromide⁵²

10 mmol of benzoic acid was dissolved in excess PBr₃. The mixture was heated under reflux for *ca.* 2 h. After filtration of the orange precipitate which forms, benzoyl bromide was isolated from the mixture by distillation. It was purified by a second high vacuum distillation. Yield 75%, b.p. 46°C (0.05 mm Hg), Lit.⁵³ b.p. 48-50°C (0.05 mm).

Benzoic anhydride.^{54 a,b}

To a stirred solution of pyridine (0.1 mol in 15 cm³ of benzene), 0.05 mol of benzoyl chloride was added rapidly. The reaction is slightly exothermic and a white precipitate forms. Benzoic acid (0.05 mol) was introduced slowly. The mixture was allowed to stir for 0.5 h before filtration. Benzoic anhydride was isolated from the mixture by distillation, b.p. *ca.* 180°C (0.03mm). The yield was low *ca.* 40% due to solidification of the product in the condenser. Mpt. 42°C, Lit. mpt.⁵⁵ 45°C.

Diphenylacetyl chloride⁵⁶

0.02 mol of diphenylacetic acid and a large excess of freshly distilled SOCl_2 was heated under reflux for 1 h. The excess SOCl_2 was removed from the mixture by distillation. The acid chloride remained behind as a very viscous oil which crystallised only upon scratching. The crude acid chloride was recrystallised from petroleum ether (60-80°C) to give white crystalline diphenylacetyl chloride. Yield 92%, m.p. 53-54°C. (Lit. mpt.⁵⁶ 55°C).

Diphenylphosphinchloridate⁵⁷

A mixture of diphenylphosphinic acid (0.05 mol) and 20 cm³ of freshly distilled SOCl_2 was heated under reflux for 1 h, and then attached to a water pump and heated at 120°C for 3 h to remove the HCl and SO_2 produced. The pale yellow liquid was purified by distillation. 88% yield, b.p. 165-166°C (0.2 mm) (Lit.⁵⁷ b.p. 160-162°C (0.15 mm)).

Dimethylphosphorochloridate⁵⁸

A solution of (0.5 mol) PCl_3 in 50 cm³ of benzene was added dropwise over a 15 minute period to a stirred solution of methanol (1.5 mol) in 150 cm³ of dry benzene. The mixture was allowed to stir for 1.5 h taking care not to allow the temperature to rise above 10°C. Freshly distilled SO_2Cl_2 (0.5 mol) was then added dropwise to the mixture which was allowed to stand over-night. The benzene was evaporated under reduced pressure, and the product collected by water-pump distillation. Yield 82%, b.p. 80°C (18 mm) (Lit.⁵⁸ b.p. 55-57°C (2-3 mm)).

N-methyldialkylphosphylamidates, $Z_2P(O)NHMe$.

A large excess of dry methylamine (*ca.* 0.5 mol) was bubbled into a stirred, cooled (0-5°C) solution of $Z_2P(O)Cl$ (0.2 mol) in 80 cm³ of dry ether. The white precipitate of trimethylamine hydrochloride which formed almost immediately was filtered and the filtrate evaporated under reduced pressure. The crude product was purified by distillation.

Z=MeO: 70% yield, b.p. 70-71°C (0.2 mm) (Lit.⁵⁹ b.p. 81°C (1 mm))

¹H (CDCl₃): δ2.55 (3H, d of d, N-CH₃, J_{H,H} 6 Hz, J_{H,P} 12 Hz); δ3.69 (3H, d, O-CH₃, J_{H,P} 11 Hz); δ4.00 (1H, broad s, NH).

Z=EtO: 92% yield, b.p. 92-93°C (0.3 mm) (Lit.⁶⁰ b.p. 130°C (15 mm)).

¹H (CDCl₃): δ1.35 (6H, t, β-CH₃, J_{H,H} 7 Hz); δ2.58 (3H, d of d, N-CH₃, J_{H,H} 6 Hz, J_{H,P} 12 Hz); δ4.05 (4H, m, α-CH₂); δ3.50 (1H, broad s, NH).

Anal. calc. for C₁₂H₁₈O₄NP: C, 53.13; H, 6.69; N, 5.16%

Found: C, 53.00; H, 6.60; N, 5.01%.

N,N-dimethyldimethylphosphoramidate, ((MeO)₂P(O)NMe₂)⁶¹

Excess dry dimethylamine gas was allowed to bubble into a solution of (0.1 mol) (MeO)₂P(O)Cl in 50 cm³ of dry ether. The gas was generated by allowing an excess of a concentrated solution of dimethylamine hydrochloride to drop into aqueous sodium hydroxide. After stirring overnight, the product mixture was filtered, evaporated and pure N,N-dimethyldimethylphosphoramidate was collected by distillation under reduced pressure. 72% yield, b.p. 46-48°C (0.5 mm)

Anal. calc. for C₄H₁₂O₃NP: C, 31.37; H, 7.84; N, 9.15%

Found: C, 30.55; H, 7.90; N, 8.75%.

N-Acyl-N-methylphosphoramidates⁶, $Z_2P(O)-NMe-C(O)R'$

To a stirred mixture of finely divided sodium (0.10 mol) in 100 cm³ of dry toluene, a solution of the amide $R'C(O)NHMe$ (0.10 mol) in 15 cm³ of toluene was added dropwise over 15 mins. The mixture was heated overnight until all the sodium had disappeared to give a yellow suspension of the salt, $R'C(O)NNaMe$. The mixture was allowed to cool before adding dropwise a solution of $Z_2P(O)Cl$ in toluene, at some specific temperature (T). After stirring at this temperature for *ca.* 5 h, the mixture was filtered and the filtrate evaporated under reduced pressure. The products were isolated from the crude product mixture by chromatography or distillation.

$Z=MeO$, $R'=CH_3$ (T=40°C)

N-acetyl-N-methyldimethylphosphoramidate(IIIg) was separated from N-methylacetamide and tetra-alkylpyrophosphate in the crude product by high vacuum distillation, yield 69%, b.p. 64-66°C (0,02 mm).

¹H NMR (CDCl₃): δ2.37 (s, 3H, CH₃); δ3.05 (d, 3H, N-CH₃, J_{H,P} 8 Hz); δ3.83 (d, 6H, OCH₃, J_{H,P} 12 Hz).

Anal. calc. for C₅H₁₂NO₄P: C, 33.15; H, 6.67; N, 7.73%

Found: C, 32.80; H, 6.80; N, 7.71%.

$Z=EtO$, $R'=CH_3$ (T=5-10°C)

N-acetyl-N-methyldiethylphosphoramidate(IIIIf) was separated from the crude product mixture by column chromatography, using 20% ethyl-acetate in chloroform as eluting solvent, 35% yield.

¹H NMR (CDCl₃): δ1.38 (6H, t, β-CH₃, J_{H,H} 7 Hz); δ2.39 (3H, s, COCH₃); δ3.04 (3H, d, N-CH₃, J_{H,P} 7.5 Hz); δ4.17 (4H, m, α-CH₂).

Anal. calc. for C₇H₁₆NO₄P: C, 40.19; H, 7.71; N, 6.70%.

Found: C, 39.75; H, 7.70; N, 6.55%.

Z=EtO, R'=Ph(IIIe) (T=25°C)

N-methyl-N-benzoyldiethylphosphoramidate(IIIe) was separated from the crude product mixture by column chromatography, eluting with 20% ethyl-acetate in chloroform, 40% yield.

^1H NMR (CDCl_3): δ 1.20 (t, 6H, $\beta\text{-CH}_3$, $J_{\text{H,H}}$ 7 Hz); δ 3.15 (d, 3H, N- CH_3 , $J_{\text{H,P}}$ 8 Hz); δ 4.05 (m, 4H, $\alpha\text{-CH}_2$), δ 7.30-7.60 (m, 5H, aryl H).

Z=Ph, R'=Ph (T=10 and 45°C)

N-methyl-N-benzoyldiphenylphosphoramidate (IIIi) was separated from N-methylbenzamide in the crude product mixture by column chromatography, eluting with 25% acetone in petroleum ether (60-80°C). At T=10°C (18% yield) and at T=45°C (50% yield), m.pt 111-113°C.

^1H NMR (CDCl_3): δ 3.30 (d, 3H, N- CH_3 , J_{PNCH} 8 Hz); δ 7.50- 8.30 (m, 15H, Aromatic protons).

Anal. calc. for $\text{C}_{20}\text{H}_{18}\text{NO}_2\text{P}$: C, 71.64; H, 5.37; N, 4.17%

Found: C, 70.20; H, 5.40; N, 4.10%

MS: m/e 335 (M^+).

4.3 REACTIONS

4.3.1 Reactions discussed in chapter 2

1. Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ with PhCOCl in the presence of PhNEt_2

The reaction was carried out independently at 20, 50 and 75°C. A mixture of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ (10 mmol), PhNEt_2 (10 mmol) and PhCOCl (10 mmol) was stirred at the fixed temperature for a total period of 20 h. Fractions of the reaction mixture were withdrawn periodically, added to dry ether and then filtered to remove the diethylaniline hydrochloride. The ether was removed by distillation under vacuum and the product mixtures examined by TLC and ^1H NMR. The products were not isolated but were identified by comparison with the NMR spectra and R_f values of pure samples.

2. Reaction of $\text{Ph}_2\text{C}=\text{C}=\text{O}$ with $(\text{EtO})_2\text{P}(\text{O})\text{NHCH}_3$

To a solution of diphenylacetyl chloride (2 mmol) in 20 cm³ of ether, 2 mmol of triethylamine (in 5 cm³ of ether), was added at room temperature. The yellow precipitate of triethylamine hydrochloride which formed indicated the formation of $\text{Ph}_2\text{C}=\text{C}=\text{O}$ by dehydrochlorination of the acid chloride. After filtration of the precipitate, the diphenylketene was not isolated from the ethereal filtrate, but a solution of $(\text{EtO})_2\text{P}(\text{O})\text{NHCH}_3$ (3 mmol), in 5 cm³ of ether was added directly. The reaction was carried out at room temperature and in refluxing ether. The mixture was stirred for 1 h. The product mixture was analysed by ^1H NMR (CDCl_3) after filtration and evaporation of the solvent under reduced pressure.

3. Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NName}$ with PhCOCl in the presence of tetrabutylammonium bromide (TBAB)

A solution of $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ (60 mmol) in 100 cm³ of benzene, was added dropwise to a stirred suspension of NaH (60 mmol) and TBAB (8 mol %) in 40 cm³ of benzene. The mixture was allowed to stir at room temperature for 30 mins and then heated under reflux for the same period to ensure complete conversion to the salt, $(\text{EtO})_2\text{P}(\text{O})\text{NName}$. The gelatinous suspension was cooled to low temperature (6-8°C) before a solution of freshly distilled PhCOCl (60 mmol) in 30 cm³ of benzene was added dropwise over a 15 min. period. After 0.5 h at this temperature, a sample of the reaction mixture was removed. The sample was worked up by filtration and evaporation of benzene under reduced pressure and the product mixture was examined by TLC and ¹H NMR. Monitoring in this way was repeated after 0.5 h at room temperature and then at regular intervals over a 46 h period of heating under reflux.

After filtration and evaporation, the final product mixture was separated by chromatography, eluting with 20% ethylacetate in chloroform.

Fraction 1

Ethylbenzoate, 26% yield, $R_f=0.71$.

¹H NMR (CDCl_3): $\delta 1.33$ (3H, t, $J_{\text{H,H}}$ 7 Hz, $\beta\text{-CH}_3$); $\delta 4.33$ (2H, q, $J_{\text{H,H}}$ 7 Hz, $\alpha\text{-CH}_2$); $\delta 7.25\text{--}7.50$ (3H, m, meta and para Ph); $\delta 8.03$ (2H, d of d, J_{ortho} 8 Hz, J_{meta} 2 Hz, ortho Ph).

MS: m/e 150 (M^+).

Fraction 2

N-methyldibenzimide, 22% yield, Rf=0.68.

^1H NMR (CDCl_3): δ 3.50 (3H, s, N-CH₃); δ 7.10-7.30 (6H, m, meta and para Ph); δ 7.50 (4H, d of d, J_{ortho} 8 Hz, J_{meta} 2 Hz, ortho Ph).

m.p. 97-98°C

Anal. calc. for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 75.29; H, 5.50; N, 5.85%

Found: C, 75.30; H, 5.40; N, 5.80%.

MS: m/e 239 (M^+).

Fraction 3

N-methylbenzamide, 13% yield, Rf=0.237.

^1H NMR (CDCl_3): δ 2.98 (3H, d, N-CH₃, $J_{\text{H,H}}$ 5 Hz); δ 6.9 (1H, broad s, NH); δ 7.33-7.66 (3H, m, meta and para Ph), δ 7.90 (2H, d of d, J_{ortho} 8 Hz, J_{meta} 2 Hz, ortho Ph).

Anal. calc. for $\text{C}_8\text{H}_9\text{NO}$: C, 71.09; H, 6.71; N, 10.36%

Found: C, 69.33; H, 6.70; N, 9.54%.

m.p. 76-77°C (lit⁶² m.p. 75°C).

MS: m/e 135 (M^+).

Fraction 4 (Benzoic acid)

Identified from melting point and mixed melting point analysis.

4. Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ with $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$

To a stirred suspension of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ (12 mmol) and TBAB (5 mol %) in 20 cm³ of toluene, a solution of $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (12 mmol) in 5 cm³ of toluene was added dropwise over a period of 15 min. at room temperature. The mixture was heated under reflux with stirring for 12 h. After cooling, the mixture was filtered and the solvent evaporated under reduced pressure. The product mixture separated by column chromatography using a chloroform-acetone (1:1) mixture as eluent. The following products were isolated and identified by ¹H NMR.

Fraction 1

Triethylphosphate, 8% yield.

¹H NMR (CDCl_3): δ 1.35 (9H, t, β -Me, $J_{\text{H,H}}$ 7 Hz); δ 4.12 (6H, q, α -CH₂, $J_{\text{H,H}} = J_{\text{H,P}}$ 7 Hz).

MS: m/e 182 (M^+).

Fraction 2

N-methyl tetraethylimidophosphate, 55% yield.

¹H NMR (CDCl_3): δ 1.38 (12H, t, β -CH₃, $J_{\text{H,H}}$ 7 Hz); δ 2.96 (3H, t, N-Me, $J_{\text{H,P}}$ 9.5 Hz); δ 4.20 (8H, m, α -CH₂).

Anal. calc. for $\text{C}_9\text{H}_{23}\text{NO}_6\text{P}_2$: C, 35.65; H, 7.65; N, 4.62%

Found: C, 35.55; H, 7.60; N, 4.55%.

MS: m/e 303 (M^+).

Fraction 3

Unreacted $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ (ca. 35%).

5. Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}(\text{IIIe})$ with nucleophiles, Y
($\text{Y}=\text{PhC}(\text{O})\text{NMe}$, $(\text{EtO})_2\text{P}(\text{O})\text{NMe}$, EtO^- , MeO^- , Cl^- , Br^- ,
 HSO_4^- and EtOH).

The sodium alkoxides were prepared by dissolving the required amount of sodium in alcohol and evaporating the excess alcohol under reduced pressure. Sodium salts of N-methylbenzamide and N-methyl diethylphosphoramidate were prepared as described before. Chloride was used as NaCl, or as a NaCl/TBAB mixture. Bromide and hydrogen sulphate was used as TBAB and $\text{Bu}_4\text{N}^+\text{HSO}_4^-$ respectively.

10 mmol of the sodium salt NaY (or EtOH) was introduced into a stirred solution of 10 mmol (IIIe) and 8 mol % of TBAB in 40 cm³ of benzene at 6°C. After 0.5 h at this temperature, a sample of the reaction mixture was removed. It was analysed by TLC and ¹H NMR after filtration and evaporation under reduced pressure. The reaction mixture was also analysed in this way after 0.5 h at room temperature and then at regular intervals over a prolonged period of heating under reflux. The overall time of heating varied with the nature of Y, as the reactions proceed at different rates. In each case, the products were not isolated from the final reaction mixtures but identified by comparison with the ¹H NMR spectra and the R_f values of authentic samples of possible products of the reactions.

6. Preparation of $\text{Me}_4\text{N}^+(\text{RR}'\text{N})(\text{MeO})\text{PO}_2^-$

A solution of $(\text{MeO})_2\text{P}(\text{O})\text{NRR}'$ (1 mmol) and triethylamine (*ca.* 1.5 mmol) in 5 cm³ of dry acetonitrile was heated in a sealed tube at 70-80°C for about 12 h. The white precipitate was filtered and identified by ¹H NMR (D₂O) due to the characteristic signals of Me_4N^+ (δ 3.19, s, 12H) and the remaining ester group (δ 3.54, d, $J_{\text{H,P}}$ 12 Hz, 3H). These salts were used directly for further reactions.

7. Reaction of $\text{Me}_4\text{N}^+(\text{RR}'\text{N})(\text{MeO})_2\text{PO}_2^-$ (R=Me; R'=Me; MeC(O)) with PhCOCl.

A solution of 1 mmol of PhCOCl in 10 cm³ of acetonitrile was added to the freshly prepared salt (1 mmol) and the mixture was heated under reflux for *ca.* 4 h. After filtration and evaporation of the solvent under reduced pressure, the product mixture was separated by column chromatography, eluting with a 20% acetone in chloroform mixture.

R=Me; R'=Me

N,N-dimethylbenzamide, 65% yield.

MS: m/e 149 (M^+); 105 (PhCO^+); 77 (Ph^+); 51 (C_4H_3^+); 44 ($\text{C}_2\text{H}_4\text{NH}_2^+$).

Anal. calc. for $\text{C}_8\text{H}_{11}\text{NO}$: C, 72.45; H, 7.43; N, 9.39%

Found: C, 71.55; H, 7.30; N, 9.04%.

m.p. 39-40°C (Lit.⁶³ m.p. 41-42°C).

R=Me, R'=MeCO

N-acetyl-N-methylbenzamide, 78% yield.

Anal. calc. for $\text{C}_{10}\text{H}_{11}\text{NO}_2$: C, 67.78; H, 6.26; N, 7.91%.

Found: C, 67.20; H, 6.30; N, 7.75%.

8. Reaction of $(\text{MeO})_2\text{PO}_2\text{Na}$ with PhCOCl

A mixture of anhydrous $(\text{MeO})_2\text{PO}_2\text{Na}$ (2 mmol), PhCOCl (2 mmol) and TBAB (5 mol %) in 10 cm³ of benzene was heated under reflux for 2 h. After filtration and evaporation of solvent, the reaction mixture was separated by column chromatography using chloroform as eluting solvent, yielding benzoxyldimethylphosphate (40%).

¹H NMR (CDCl_3): δ 4.07 (6H, d, $J_{\text{H,P}}$ 13 Hz, $\text{P}(\text{O})\text{Me}$); δ 7.6-7.8 (3H, m, meta and para Ph); δ 8.2 (2H, d of d, ortho Ph). MS: m/e 230 (M^+); 105 (PhCO^+); 77 (Ph^+); 51 (C_4H_3^+).

9. Reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ with PhCOX ($\text{X}=\text{F}$, Cl , Br and PhCOO^-) in the absence of TBAB.

A solution of PhCOX (15 mmol) in 5 cm³ of benzene was added dropwise to a stirred suspension of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ in 30 cm³ of benzene at room temperature. After 0.5 h a sample was removed from the reaction mixture. The sample was analysed by TLC and ¹H NMR after filtration and evaporation. The remaining reaction mixture was refluxed for *ca.* 17 h before analogous work-up and analysis.

The products were not isolated from the final product mixture but were identified by comparison with ¹H NMR spectra and R_f values of authentic samples of possible products of the reactions. In all cases no $(\text{EtO})_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$ was observed in the final product mixture.

The relative concentrations of the different products were calculated from a comparison of the integration ratios of their protons.

In an independent experiment, a benzene solution of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ and PhCOCl was heated under reflux in an apparatus in which the reflux condenser was connected by a teflon tube with a trap containing CD_2Cl_2 cooled in a dry ice-acetone bath. The ^1H NMR spectra of the CD_2Cl_2 solution were recorded at -50°C after 1 h and 4 h of refluxing the reaction mixture. For both solutions a considerable quantity of ethyl chloride was observed $\delta 1.50$ (3H, t, $J_{\text{H,H}}$ 8 Hz); $\delta 3.64$ (2H, q, $J_{\text{H,H}}$ 8 Hz).

10. Competitive reaction of $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ with $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ and $\text{PhC}(\text{O})\text{NNaMe}$.

$(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ (4 mmol) and $\text{PhC}(\text{O})\text{NNaMe}$ (4 mmol) were prepared in benzene as previously described. These salts were combined. To the stirred suspension a solution of $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (4 mmol) in 5 cm^3 of benzene was added dropwise. The mixture was heated under reflux for 1.5 h and then filtered and evaporated under reduced pressure. The products present in the final mixture, were identified from the ^1H NMR spectrum (CDCl_3). $\text{PhC}(\text{O})\text{NHMe}$ was present in high concentration, $(\text{EtO})_2\text{P}(\text{O})\text{NHMe}$ in low concentration and $[(\text{EtO})_2\text{P}(\text{O})]_2\text{NMe}$ in moderate concentration. The latter compound was identified by its distinctive N-methyl triplet at $\delta 2.94$, (3H, t, $J_{\text{H,P}}$ 9.5 Hz, N-Me).

11. Competitive reaction of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ with $\text{PhC}(\text{O})\text{Cl}$ and $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$

Equimolar amounts of $\text{PhC}(\text{O})\text{Cl}$ (3 mmol) and $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (3 mmol), each dissolved in 5 cm³ of benzene, were added to a stirred suspension of $(\text{EtO})_2\text{P}(\text{O})\text{NNaMe}$ (3 mmol) in 30 cm³ of benzene. After heating under reflux for 1.5 h and work-up as before, the product mixture was examined by ¹H NMR spectroscopy. The spectrum showed PhCO_2Et to be the major product with only a small amount of $\text{PhC}(\text{O})\text{NHMe}$. Both $[(\text{EtO})_2\text{P}(\text{O})]_2\text{NMe}$ and $(\text{EtO})_2\text{P}(\text{O})-\text{NMe}-\text{C}(\text{O})\text{Ph}$ were absent from the final product mixture.

4.3.2 REACTIONS DISCUSSED IN CHAPTER 3

1. Reaction of $\text{R}'\text{MgX}$ with $(\text{RO})_2\text{P}(\text{O})-\text{NMe}-\text{C}(\text{O})\text{CH}_3$ ($\text{R}'=\text{Ph}, \text{Me}$; $\text{R}=\text{Et}, \text{Me}$).

To prepare phenylmagnesium bromide, 22 mmol of freshly distilled bromobenzene in about 10 cm³ of dry ether was added dropwise to 22 mmol of washed and dried magnesium turnings in 30 cm³ of refluxing ether. After stirring for about 3 h the formation of PhMgBr was complete and no unreacted magnesium turnings remained. Methylmagnesium iodide was prepared in the same way.

An ether solution of $(\text{RO})_2\text{P}(\text{O})-\text{NMe}-\text{C}(\text{O})\text{CH}_3$ (the concentration of which varied with R, R'), was added dropwise to the Grignard reagent at room temperature. The reaction was highly exothermic and a white precipitate formed immediately. The mixture was allowed to stir for 1.5 h before quenching with

a concentrated aqueous solution of either ammonium carbonate (30 g in 100 cm³) or potassium carbonate (30 g in 100 cm³). The white precipitate dissolved and after stirring for a further 0.5 h, the two layers were separated. The aqueous layer was further extracted with 3 x 15 cm³ of ether and all the fractions combined. Only the ether layer was analysed by ¹H NMR and TLC after evaporation of ether under reduced pressure.

For R=Me; R'=Me, the reaction was repeated on a larger scale, (approximately 50 mmol of substrate was used), and the reaction mixture analysed without prior aqueous work-up. Once the reaction had gone to completion, the mixture was allowed to stir in an open flask until all the ether had evaporated spontaneously and only a white precipitate remained. A fraction of this precipitate was allowed to digest in CDCl₃ overnight. After centrifuging, an ¹H NMR spectrum of the supernatant CDCl₃ solution was recorded. The ¹H NMR spectra of this same fraction was also recorded after spiking successively with acetone and methanol.

For R'=Ph, R=Et:

The molar ratio of mixed-imide to Grignard reagent was 1:1. After filtration and evaporation of ether, the final product mixture was separated by column chromatography, eluting with a 10% ethyl-acetate in chloroform mixture. Only three pure fractions were obtained in high enough concentration to be identified by their ¹H NMR spectra.

Fraction 1

Unreacted bromobenzene.

Fraction 2

Diphenylmethyl carbinol, 50% yield, m.p. 80-81°C (lit.⁶⁴ m.p. 80-81°C).

¹H NMR (CDCl₃): δ1.93 (3H, s, CH₃); δ2.73 (1H, broad s, OH); δ7.2- 7.6 (10H, m, ortho and meta Ph).

Anal. calc. for C₁₄H₁₄O: C, 84.85; H, 7.07%

Found: C, 84.51; H, 7.01%.

Fraction 3

Unreacted N-methyl-N-acetyldiethylphosphoramidate, identified by comparison with authentic sample.

For R'=Me, R=Me

The molar ratio of the mixed-imide to Grignard reagent was 1:2. The products were not isolated but identified in the ¹H NMR spectrum of the final product mixture by comparison with spectra of authentic samples. The major product is t-butanol; δ1.3 (9H, s, -CH₃); δ1.7 (1H, broad s, OH).

2. Reaction of R'MgX with (MeO)₂P(O)NMe₂ (R'=Ph, Me)

Methylmagnesium iodide and phenylmagnesium bromide were prepared as before from methyl iodide and bromobenzene respectively.

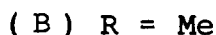
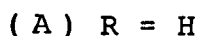
A solution of (MeO)₂P(O)NMe₂ (11 mmol) in 10 cm³ of ether was added dropwise at room temperature to 22 mmol of the Grignard reagent in 30 cm³ of ether. The reaction was only slightly exothermic and no precipitate formed. On work-up with 50 cm³ of ammonium chloride solution (R'=Ph) or potassium carbonate solution (R'=Me), extreme effervescence was observed as the largely unreacted Grignard reagent was hydrolysed. The two layers were separated and aqueous layer washed with 3 x 15 cm³ of ether. The ether fractions were combined and dried over magnesium sulphate. After filtration and evaporation of ether under reduced pressure, the final product mixture was analysed by ¹H NMR spectroscopy.

Appendix

APPENDIX

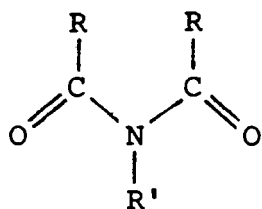
The crystal and molecular structure of $(\text{MeO})_2\text{P}(\text{O})-\text{NH}-\text{C}(\text{O})\text{Ph}^5$ (IIIh) have provided information on the planarity of the OPNCO fragment, the intramolecular hydrogen bonding pattern as well as the preferred conformation of both the amide systems. We have already commented on some of these aspects.

Without entering into detail, we comment further on some pertinent findings of a recent comparative structural study of dibenzimide (A) and N-methyldibenzimide (B).⁴⁶

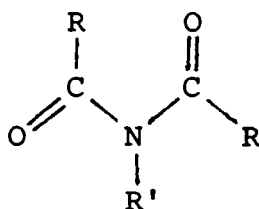


An important consequence of N-methylation of (A) is the distortion of the planarity of the OCNCO moiety, which in turn, reduces the conjugation of the nitrogen non-bonding electrons with the adjacent carbonyl centres. As a result the N-C bond lengths in the N-methylated-derivative are longer than in (A).

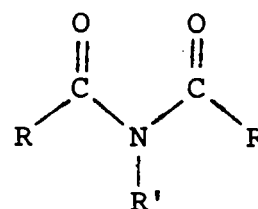
N-methylation of (A) also gives rise to interesting conformational changes. There are three conformational possibilities for the symmetrical imide $(\text{RCO})_2\text{NR}'$, viz. (E,E; E,Z; Z,Z).



(E,E)



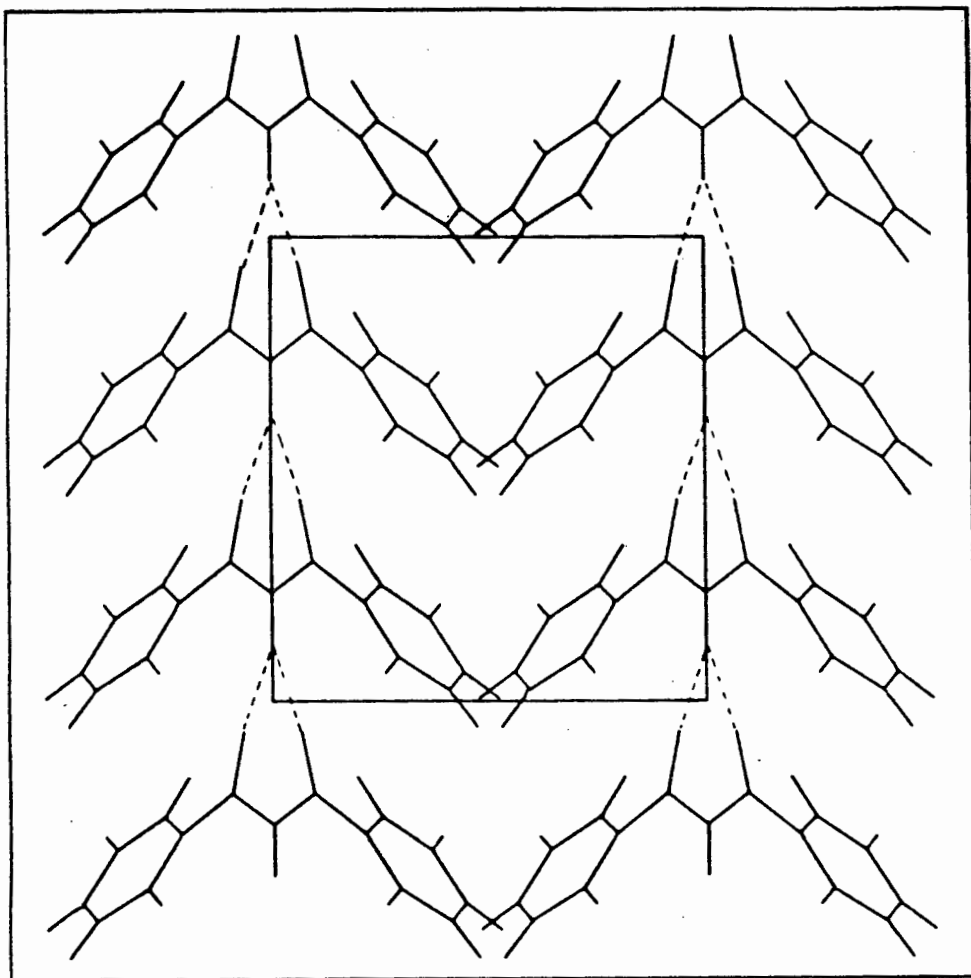
(E,Z)



(Z,Z)

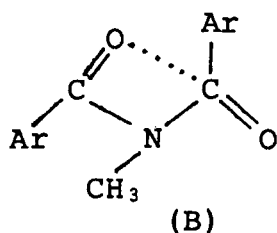
The conformation of (A) that prevails in the solid state is approximately (Z,Z). The stability of this form arises from the possibility of hydrogen bonding between the imido hydrogen and the carbonyl oxygens as illustrated by the crystal packing of the molecules in Figure (4)

Figure 4



For (B), intramolecular steric interactions between the methyl and ortho aromatic hydrogens destabilize the (Z,Z) conformation, and an (E,Z) arrangement is the only possible choice. For both (A) and (B), the conformations are only approximations to the ideal situations. Another interesting feature of the molecular structure of (B) is the incipient $O \cdots C=O$ contact that exists within the molecules (Structure B).

Structure B



The distance between the carbonyl oxygen and the other carbonyl carbon is 2.788(5) Å, which is shorter than the sum of the V.d. Waals radii of these two elements.

Our interest in the crystal and molecular structure of N-methyl-N-benzoyldiphenylphosphinamidate(IIIi) is two-fold. Firstly, we wished to study the changes in conformational preference when proceeding from a secondary to a tertiary mixed-imide as reported⁴⁶ for (A) and (B). Unfortunately, the N-methyl analogue of (IIIh) is non-crystalline⁴⁷ and (IIIi) is the first crystalline tertiary mixed-imide that we have been able to prepare and was thus used for the purpose of this study. Also of interest to us is the structural differences between (IIIi) and its carbonyl analogue (B).

Ph₂P(O)-NMe-C(O)Ph(IIIi) was prepared via the N-phosphorylation of N-methylbenzamide anion at 45°C according to the procedure previously discussed (section 2.1). The overall yield of (IIIi) was 50% as opposed to 18% when the reaction was performed at 10°C. Unreacted N-methylbenzamide anion was separated⁴⁸ from the product by column chromatography using a petroleum ether/acetone mixture (3/1) as eluting solvent. However, as the R_f values of (IIIi) and N-methylbenzamide remained relatively close, only a small fraction of the pure product was obtained, initially as an oil which then forms white crystals on cooling, mpt. 111-113°C.

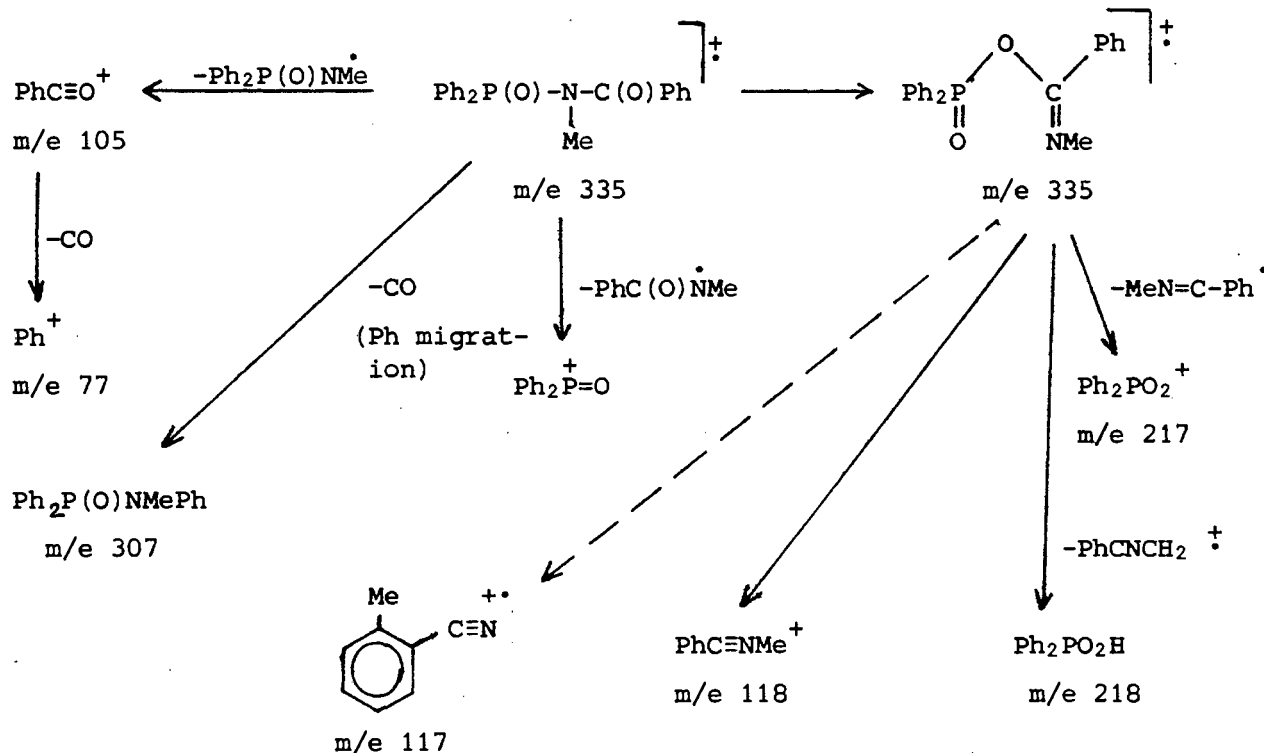
Anal. Calc. for $C_{20}H_{18}O_2NP$: C, 70.28; H, 5.40; N, 4.10%.

Found: C, 71.64; H, 5.37; N, 4.17%.

The product was further identified by 1H NMR and mass spectrometry. 1H NMR ($CDCl_3$); δ 3.17 (3H, d, N-Me, $J_{PNCH} = 8$ Hz), δ 7.5- 8.3 (15H, m, Ar-H).

The fragmentation pattern which we propose in Scheme 18 to account for the major peaks in the spectrum (Figure 4), is similar to those outlined⁶ for related compounds.

Scheme 18



The spectrum also contains a peak at m/e 418 which can be explained in terms of the thermal dehydration of phosphinic acid to yield the anhydride system (IVa), equation (i).

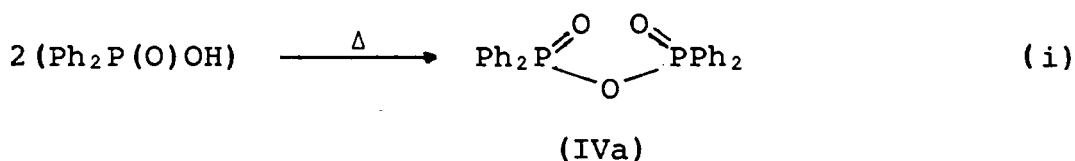
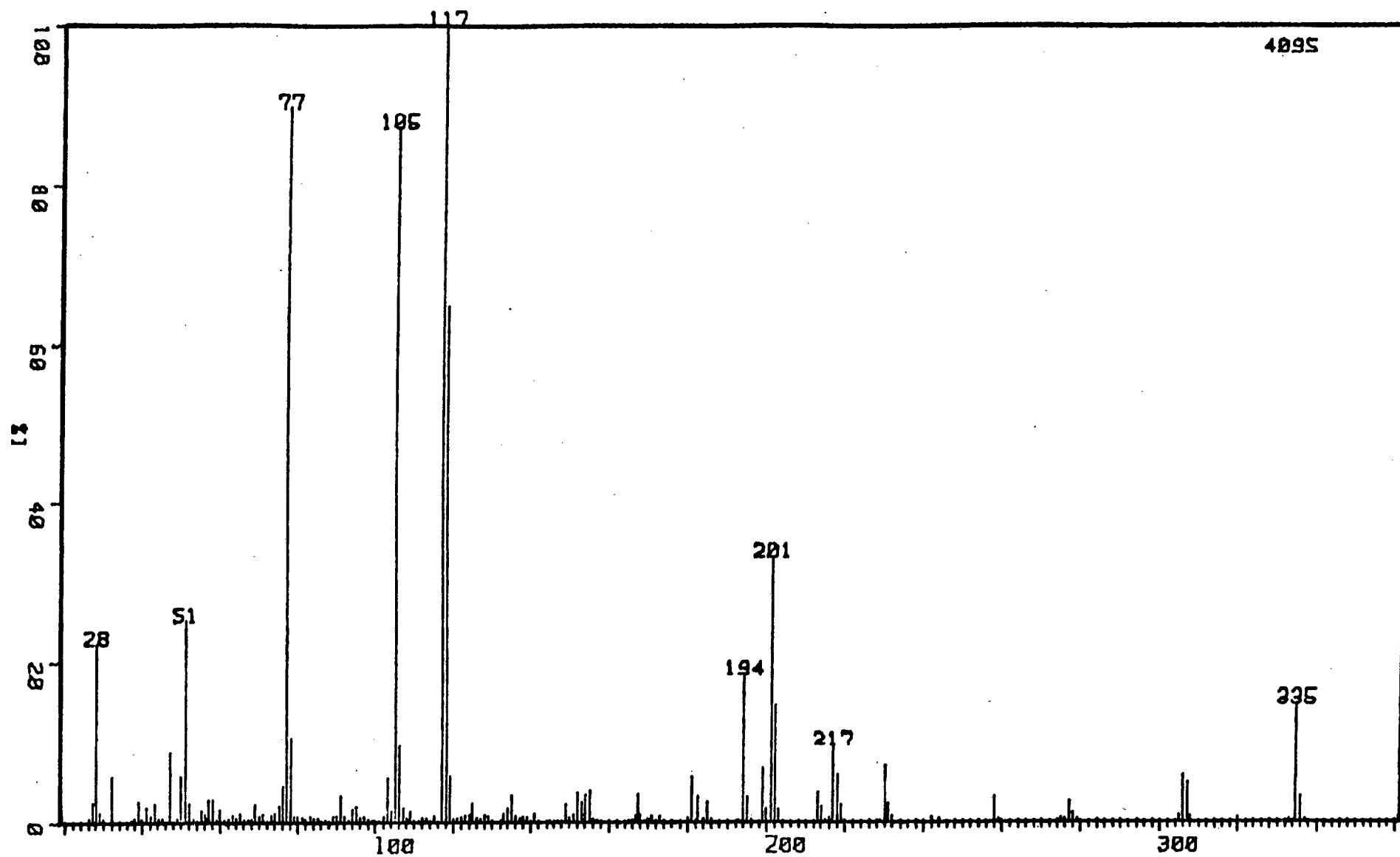


Figure 5: Mass Spectrum of $\text{Ph}_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$



It is interesting to note that m/e 105 > 201 which implies that N-C cleavage is more favourable than P-N cleavage. This is most probably due to the greater stability of the benzoylium ion PhCO^+ over the phosphacylium ion, Ph_2PO^+ .

$\text{Ph}_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$ was crystalized as long needles from petroleum ether (60-80°C)/acetone (4:1). Diphenylphosphinic acid crystalized from the same solution indicating that slow hydrolysis occurs during crystalization over a prolonged period of time. Because of the different shape of the $\text{Ph}_2\text{P}(\text{O})\text{OH}$ crystals (small hexagons), these could readily be separated by hand from (IIIIi) and were identified by their mpt. 193-194°C. (Lit.^{5,3} mpt. 194-195°C). The identity of the needle-shaped crystals was confirmed by their melting point and fragmentation pattern.

Preliminary photography established that (IIIIi) had crystalised in a monoclinic lattice. The approximate unit cell dimensions, together with the estimate of the crystal density gave $Z=8$.

Accurate cell constants were obtained for (IIIIi) by least squares settings of 25-high order reflections measured on a Philips PW1100 four-circle diffractometer with graphite monochromated $\text{Mo-K}\alpha$ ($\lambda=0,7107 \text{ \AA}$) radiation. Crystal data and experimental details of the data collections are listed in Table 3.

Table 3

Crystal data and experimental and refinement parameters for compound (IIIi)

<u>Crystal data</u>	<u>Ph₂P(O)-NMe-C(O)Ph</u>
Molecular formula	C ₂₀ H ₁₈ O ₂ NP
Mr	335,34
Space group	P2 ₁ /m
a/Å	13,460 (7)
b/Å	20,72 (1)
c/Å	6,161 (3)
β/°	103,22°C (2)
V/Å ³	1673,0
D _c /Mgm ⁻³ (for Z=4)	1,33
F(000)	704,00

Data collection

Crystal dimension (mm)	0.15 x 0.05 x 0.075
Scan mode	ω-2θ
Scan width/°θ	0.9
Scan speed/° θs ⁻¹	0.359
Range scanned (2θ)/°	6-44
Number of reflections collected	2441

The most apparent systematic absences of the OkO (k=2n+1) reflections indicated that the space-group was either (P₂₁/m) or P₂₁. However, P₂₁ is unlikely because it is non centrosymmetric and it has Z=2.

Because of the poor quality of the crystals the reflections in the data set were very weak and we were unable to solve the structure using the direct-methods centrosymmetric package of SHELX-76.⁶⁵

However, new attempts are being made to solve the structure and we are optimistic that the results will be published in the near future.

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48. The synthesis was carried out on a small scale, and after stirring for 0.5 h, $\text{PhC}(\text{O})\text{Cl}$ was added in an attempt to convert the unreacted N-methylbenzamide anion to N-methyldibenzimide. The R_f value of the latter differs considerably from that of $\text{Ph}_2\text{P}(\text{O})\text{-NMe-C}(\text{O})\text{Ph}$, and separation by chromatography is expected to be easier. However, as this secondary reaction was only marginally successful, it was not repeated in the large scale synthesis.

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